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1 Kaa<sub>1</sub> Xaa<sub>2</sub> Xaa<sub>3</sub>Gly Thr Xaa<sub>4</sub> Xaa<sub>5</sub> Xaa<sub>6</sub> Xaa<sub>8</sub> Ser Lys Gin Xaa<sub>9</sub>Glu Glu Glu Ala Val Arg Leu Xaa<sub>15</sub>Xaa<sub>16</sub>Xaa<sub>17</sub>Xaa<sub>18</sub>-Z Ala Ala GIŞ 25 Xaa<sub>10</sub> Xaa<sub>11</sub> Xaa<sub>12</sub> Xaa<sub>13</sub> Leu Lys Asn Gly Gly Xaa<sub>14</sub> Ser Ser

Ser Ser Pro Ser Phe Pro Pro Pro Ser PhelPro Pro Pro Ser Trp | Pro | Pro | Pro | Ser Trp | Pro | Pro | Pro | Ser Ser Ser Ser Pro Ser Pro Pro Ser Ser Ser Ser |Xaa<sub>12</sub>|Xaa<sub>3</sub>|Xaa<sub>4</sub>|Xaa<sub>15</sub>|Xaa<sub>16</sub>|Xaa<sub>17</sub>|Xaa<sub>1</sub> Pro Trp Pro Pro Pro Glu Trp Pro Pro Phe Pro Pro Pro Pro Trp Pro Pro Phe Pro Pro Pro Pro Pro Pro Pro Trp Trp Tro Trp ع G Glu Glu a B B 35 35 35 Glu Glu Glu <u>G</u> Glu Olu Olu Glu Glu Glu |Xaa<sub>5</sub>|Xaa<sub>6</sub> |Xaa<sub>7</sub> |Xaa<sub>8</sub> |Xaa<sub>9</sub>|Xaa<sub>10</sub> |Xaa<sub>11</sub> Phelile Ser Asp Leu Met Phe IIe Ser Asp Leu Met Phe IIe Phe IIe Leul Phe IIe Phe IIe Ser Asp|Leu|Met|Phe|Ile Asp Leu Met Phe IIe Glu Leu Met Phe Ile Phe Ile Asp|Leu|Met|Phe|Val Ser| Asp|Leu | Met| Phe|Ile Ser| Asp|Leu | Met| Phe|Ile Phelile Asp Leu pGly Phe Ile Ser Asp Leu pay Phe IIe Asp|Leu|Methaph|Ile Met Leu Asp|pGly|Met Leu Met AsppGly Leu Leu Ser|Asp|Leu| Leu Ser Asp Asp Asp Ser T Ser Ser Ser Thr Ser Ser Ser | Phe Thr PheThr PheThr Glu PhelThr Phe Thr Gly Glu Phe Thr Phe Thr Glu Phe Thr Glu naph Thr Glu Phe Ser Glu Phe Thr Glu Phe Thr Glu Phe Thr Glu Phe Ser Phe 1 Xaa, Xaa<sub>2</sub> Xaa<sub>3</sub> Xaa<sub>4</sub> Glu Glu Glu His Gly Glu Asp Glu Glu Gla Gly <u>S</u> G Gly Gly GIV <u>S</u> Gly <u>≥</u> G Gi Gly His Gly E.S. His His His His His His His His H:S His 100 [12] 13 [14] [15] 16] <u>7</u> [6] 20 [22] [24] [25] 16 ന D,  $\infty$  $\sim$ က 2 9 တ 4

Fig. 3A



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| aa <sub>3</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>5</sub> Xaa <sub>7</sub> Xaa <sub>8</sub> Xaa <sub>9</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>3</sub> Xaa <sub>4</sub> Xaa <sub>4</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>5</sub> Xaa <sub>5</sub> Xaa <sub>9</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>2</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>2</sub> Xaa <sub>2</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>2</sub> Xaa <sub>2</sub> Xaa <sub>2</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>2</sub> Xaa <sub>2</sub> Xaa <sub>2</sub> Xaa <sub>1</sub> Xaa <sub>2</sub> Xaa <sub>2</sub> Xaa <sub>1</sub> Xaa <sub>2</sub> Xaa <sub>2</sub> Xaa <sub>2</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>2</sub> Xaa <sub>2</sub> Xaa <sub>2</sub> Xaa <sub>2</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>2</sub> Xaa | •                 | ٠,       |      |      |     |     |        |           |          |   | 2    |          |          |          |                   |
|--|-------------------|----------|------|------|-----|-----|--------|-----------|----------|---|------|----------|----------|----------|-------------------|
| ixaa, xaa <sub>2</sub> xaa <sub>3</sub> xaa <sub>4</sub> xaa <sub>5</sub> xaa <sub>6</sub> xaa <sub>7</sub> xaa <sub>9</sub> xaa <sub>9</sub> xaa <sub>9</sub> xaa <sub>1</sub> xaa <sub>2</sub> xaa <sub>2</sub> xaa <sub>3</sub> xaa <sub>4</sub> xaa <sub>5</sub> xaa <sub>5</sub> xaa <sub>5</sub> xaa <sub>1</sub> xaa <sub>1</sub> His Gly Glu Phe Thr Ser Asp Leu Met Phelta Glu Phe Pro Pro Pro Ser His Gly Glu Phe Thr Ser Asp Leu Met Phelta Glu Phe Pro Pro Pro Pro Ser His Gly Glu Phe Thr Ser Asp Leu Met Phelta Glu Pro Pro Pro Pro Ser His Gly Glu Phe Thr Ser Asp Leu Met Phelta Glu Trp Pro thro thro thro Ser His Gly Glu Phe Thr Ser Asp Leu Met Phelta Glu Trp Pro thro thro thro Ser His Gly Glu Phe Thr Ser Asp Leu Met Phelta Glu Trp Pro thro thro thro Ser His Gly Glu Phe Thr Ser Asp Leu Met Phelta Glu Trp Pro thro thro thro Ser His Gly Glu Phe Thr Ser Asp Leu Leu Phelta Glu Trp Pro thro thro thro Ser His Gly Glu Phe Thr Ser Asp Leu Leu Phelta Glu Phet Thro thro thro thro thro thro Ser His Gly Glu Phe Thr Ser Asp Leu Leu Phelta Glu Trp Mealmealameala Ser His Gly Glu Phe Thr Ser Asp Leu Leu Phelta Glu Trp Mealamealameala Ser His Gly Glu Phe Thr Ser Asp Leu Met Phelta Glu Trp Mealamealameala Ser His Gly Glu Phe Thr Ser Asp Leu Met Phelta Glu Trp Mealamealameala Ser His Gly Glu Phe Thr Ser Asp Leu Met Phelta Glu Trp Mealamealameala Ser His Gly Glu Phe Thr Ser Asp Leu Met Phelta Glu Trp Mealamealamealameala Ser His Gly Glu Phe Thr Ser Asp Leu Met Phelta Glu Trp Pro Mealamealamealameala Ser His Gly Glu Phelth Ser Asp Leu Leu Phelta Glu Trp Pro Mealamealamealamealamealamealamealameala  | Z                 | NH2      | NH2  | NH2  | NH2 | NH2 | NH2    | NH2       | NH2      | NH2   | NH2  | NH2      | NH2      |          | . NH <sub>2</sub> |
| Kaa, Xaa <sub>2</sub> Xaa <sub>3</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>5</sub> Xaa <sub>9</sub> Xaa <sub>9</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>2</sub> Xaa <sub>3</sub> Xaa <sub>4</sub> Xaa <sub>3</sub> Xaa <sub>4</sub> Xaa <sub>3</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>5</sub> Xaa <sub>5</sub> Xaa <sub>7</sub> Xaa <sub>1</sub> Xaa <sub>1</sub> Xaa <sub>2</sub> Xaa <sub>3</sub> Xaa <sub>4</sub> Xaa <sub>3</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>5</sub> Xaa <sub>5</sub> Xaa <sub>7</sub> His Gly Glu Phe Thr Ser Asp Leu Leu Phelbug Glu Trp Pro Pro Pro Pro His Gly Glu Phe Thr Ser Asp Leu Met Phelle Glu Phe Pro Pro Pro Pro His Gly Glu Phe Thr Ser Asp Leu Met Phelle Glu Trp Pro Pro Pro Pro His Gly Glu Phe Thr Ser Asp Leu Met Phelle Glu Trp Pro Itpro Itpro Itpro Itpro His Gly Glu Phe Thr Ser Asp Leu Met Phelle Glu Trp Pro Itpro Itpro Itpro His Gly Glu Phe Thr Ser Asp Leu Met Phelle Glu Trp Pro Itpro Itpro Itpro Itpro His Gly Glu Phe Thr Ser Asp Leu Met Phelle Glu Trp Pro Itpro Itpr   | Xaa <sub>18</sub> | Ser      | Ser  | Ser  | Ser | Ser | S      | Ser       | Ser      |   | Ser  |          | Ser      | Ser      | Sel               |
| Xaa, Xaa <sub>2</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>6</sub> His Gly Glu Phe Thr Ser   | (aa <sub>17</sub> | Pro      | Pro  | Pro  | Pro | Pro | tPro   | tPro      | hPro     | hPro  | tPro | hPro     | MeAla    | MeAla    | MeAla             |
| Xaa, Xaa <sub>2</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>6</sub> His Gly Glu Phe Thr Ser   | (aa <sub>16</sub> | Pro      | Pro  | Pro  | Pro | Pro | Pro    | tPro      | hPro     | hPro  | tPro | h<br>Pro | MeAla    | MeAla    | MeAla             |
| Xaa, Xaa <sub>2</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>6</sub> His Gly Glu Phe Thr Ser   | Xaa <sub>15</sub> | Pro      | Pro  | Pro  | Pro | Pro | Pro    | tPro      | hPro     | hPro  | tPro | hPro     | MeAla    | MeAla    | MeAla             |
| Xaa, Xaa <sub>2</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>6</sub> His Gly Glu Phe Thr Ser   | Xaa <sub>4</sub>  | 5<br>2   | Pro  | 20   | Pro | Pro | tPro   | Pro       | hPro     | Pro   | tPro | hPro     | MeAla    | Pro      | MeAla             |
| Xaa, Xaa <sub>2</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>6</sub> His Gly Glu Phe Thr Ser   | Xaa <sub>13</sub> | Phe      |      | Phe  |     | Phe |        |           |          | Trp   | Phe  | Phe      | 르        |          | Phe               |
| Xaa, Xaa <sub>2</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>6</sub> His Gly Glu Phe Thr Ser   | Xaa <sub>12</sub> |          | Glu  | Glu  | Asp | Glu | Glu    | Glu       | Glu      | Glu   | Glu  | Glu      | Glu      | Glu      | Glu               |
| Xaa, Xaa <sub>2</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>6</sub> His Gly Glu Phe Thr Ser   | Xaa               | Val      | tBuG | tBuG | Ile | Ile | Ile    | Ile       | Ile      | Ile   | Ile  | lle      | Ile      | əII      | Ile               |
| Xaa, Xaa <sub>2</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>6</sub> His Gly Glu Phe Thr Ser   | Xaa <sub>10</sub> | Phe      |      |      |     | Phe | Phe    | Phe       | Phe      | Phe   | Phe  |          | Phe      | bhe      | Phe               |
| Xaa, Xaa <sub>2</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>6</sub> His Gly Glu Phe Thr Ser   | Xaag              | Leu      | Met  |      | Met | Leu | Met    | Met       | Met      | Met   | Leu  |          | Met      | Met      | Leu               |
| Xaa, Xaa <sub>2</sub> Xaa <sub>4</sub> Xaa <sub>5</sub> Xaa <sub>6</sub> His Gly Glu Phe Thr Ser   | Xaa <sub>8</sub>  | ren      | ren  |      |     | Leu | Leu    | ren       |          | en en   |      | ren      | Leu      | Leu      | Leu               |
| Xaa, Xaa, Xaa, Xaa, Xaa, His Gly Glu Phe Thr<br>His Gly Glu Phe Thr   | Xaa,              | Asp      | Asp  |      | Asp |     | Asp    |           |          |   |      |          | Asp      |          | Asp               |
| Xaa, Xaa <sub>2</sub> Xaa <sub>4</sub> His Gly Glu Phe   | Xaa <sub>6</sub>  |          |      | Ser  | Ser |     |        |           |          | Ser   | Ser  |          |          |          | Ser               |
| Xaa, Xaaa, Xaaa, Xaaa, His Gly Glu   | Xaa <sub>5</sub>  | Thr      | Thr  | Thr  | Thr | Thr | Thr    | Thr       | i<br>L   | Thr   | Thr  | Į.       | Thr      | Thr      | Thr               |
| His  | Xaa4              |          |      | Phe  |     | bhe |        |           |          | Phe   | Phe  |          |          |          | Phe               |
| His  | Xaa <sub>3</sub>  |          |      |      |     | ŊŊ  |        |           |          | 35  | 믕    |          | 3        |          | Glu               |
|  | Xaa <sub>2</sub>  |          | Gly  | Gly  | Gly | Ala | G<br>G | <u>S</u>  | <u>G</u> | <u>g</u>                                      | ट्ट  |          | <u>a</u> | <u>a</u> | Gly               |
| Compound [SEG,1D,NO]  18 [27]  19 [28]  20 [29]  21 [30]  22 [31]  23 [32]  24 [33]  25 [34]  26 [35]  27 [36]  28 [37]  29 [38]  30 [39]  | Хаа,              | His      | His  | His  | His | His | Ξ      | His       | 王<br>S   | His   | His  | His      | His      | His      | His               |
| 20 Compour 18 [27] 19 [28] 20 [29] 21 [30] 22 [31] 24 [33] 25 [34] 26 [35] 27 [36] 29 [38] 30 [39]   | 25                |          | ==   |      |     |     |        | _         | _        |   |      | _        | ~        |          |                   |
| 3 3 2 2 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3  | D.O.O.            | [27      | [28  | [25  |     | 3   | [35]   | <u>86</u> | [34      | (35   | ŀ    | 3.       |          | 1        |                   |
|  | SE                | 18       | 5    | 20   | 21  | 22  | 83     | 24        | 12       | 7   | 2    | 12       | 72       | 3        | က                 |
|  | Ŀ                 | <u> </u> | L    |      | 4.  |     |        | L         | L        | <u>L.                                    </u> | L    | <u> </u> | <u> </u> |          |                   |



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| ſ          |          | -                                     | T             |            |            |             |            |            |            | <u>.</u>   |                  |                 | T               |       | :                |                 | -               | ·               |                 |                 |                 |                 |
|------------|----------|---------------------------------------|---------------|------------|------------|-------------|------------|------------|------------|------------|------------------|-----------------|-----------------|-------|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|            | 20       | -   -                                 | Arg           | Arg        | Arg        | Arg<br>Arg  | )<br>(     | ر<br>د ر   | A G        | A S        | Arg.             | Arg             | Arg             | Ara   | Ara              | A C             | Ard             | Ara             |                 | Z <             | A S             | Y d             |
|            | 6        | 3                                     | <u>a</u>      | a<br>S     | <u>a</u>   | 2 2         | g   c      | g 3        | <u>a</u> = | g -        | \<br>\<br>\<br>\ | \a<br>\         | Val             | Val   | /2               | 2/2             | le/             |                 | - 1             |                 |                 | _ [_            |
|            | 28       | \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ | Z <           | Y G        | 2 2        | N 2         | 2 2 0      | Z Z        | 2 2        | 2 2        | אַם              | Ala             | Ala             | Ala   | Ala              |                 | 1               | 1               |                 |                 | 1               | - 1             |
|            | 17       | <u>-</u>                              |               |            | ם כ        | ם מ         |            | 7          |            |            |                  |                 | 0lu             | Glu   | 9                |                 | 1               |                 |                 |                 | 1               | T               |
|            | 16       | 1                                     | $\neg \vdash$ |            | $\neg 	au$ | $\neg \neg$ |            | 7          | 1 .        |            |                  | 1               | Olu<br>Glu      | 0 00  | Glu              |                 |                 | 1               | 1               |                 | T               | - 1             |
|            | 5        | 110                                   |               |            |            |             | T          | 1          |            | - 1        |                  | - 1             |                 | 0 10  | Ala              | 1               | Olu C           | Gu              | 1               |                 | 1 '             | - 1             |
| <b> </b>   | 14       | Mat                                   |               | $\neg$     | ם כם       |             |            | - 1        |            |            |                  | - 1             | en G            | Ala G | Leu A            | 1               |                 | Leu             | ı               |                 |                 |                 |
| .          | က        | S C                                   |               |            | $\neg$     |             | 1          | 1          |            |            |                  | _               | _               |       |                  |                 |                 | 1               | 1               | 1               | _               |                 |
| -          |          | .                                     |               |            |            |             |            | 7          | Т          | 1          | 1                |                 | Ala             | 등     | n<br>U           | 등               | GI              | 띖               | g               | 1               | 1               |                 |
| Ŀ          | 12       | N N                                   |               |            | 2 \ X      | S S         | +          | 1          |            |            |                  |                 | Lys             | Lys   | Lys              | Lys             | Lys             | Lys             | L/S             | \\X             | LVS             | \ \\ \\ \\ \    |
|            | =        | Ser                                   | Se l          | S S.       | Ser        | Ser         | Ser        | Ser        | Ser        | Ala        | Spr              | 5<br>5<br>0     | Ser             | Ser   | Ser              | Ser             | Ser             | Ser             | Ser             | Ser             | Ser             | Ser             |
| L          | 9        | le l                                  | ē             | ē          | ē          | en          | Leu        | Leu        | Ala        | Leu        |                  |                 | ren             | Leu   | ren              | Leu             | Leu             | ren             | Leu             | Leu             | 1               | 1               |
|            | တ        | Asp                                   | Asp           | Asp        | Asp        | Asp         | Asp        | Asp        | 7          |            | Asn              | 2 6             | ASD             | Asp   | Asp              | Asp             | Asp             | Asp             | Asp             | Asp             | Asp             |                 |
| L          | ∞        | Ser                                   | Ser           |            |            | Ser         | Ser        | Ala        | Ser        | Ser        |                  |                 |                 |       |                  | Ser             |                 | Ser             | Ser /           | Ser /           | Ser /           | Ser             |
|            | /        | Thr                                   | Thr           | Thr        | 1          | Thr         | Thr        | Thr        | Thr        | Thr        | Thr              | ļ               | - 1             | - 1   | ij               | ig i            | Th              | Th.             | Th              | Thr             | Thr             | Thr             |
|            | ·o       | Phe                                   | Phe           |            | _          | Phe         | Ala        | Phe        | Phe        | Phe        | Phe              |                 |                 |       |                  |                 |                 |                 | Phe 1           | Phe 1           | Phe 1           | Phe 7           |
|            |          | Thr                                   | Thr           | Thr        | 1          | Ala         |            | Thr        | Thr        | 1 .        | i i              | - 1             |                 |       | - 1              | - 1             |                 |                 | hr              | 卢               | E<br>E          | 드               |
| ١,         | 4        | Gly                                   | Gly           | Gly        | Gly        | Gly /       | Gly        | Gly 1      | Gly T      | Gly        | GIV              | ) <u>}</u>      | +               |       |                  | -               |                 |                 |                 | <u> </u>        |                 | <u> </u>        |
| -          | ,        | Glu                                   | <u> </u>      | Olu O      | Glu G      |             |            | Glu G      |            |            | ĺ                | 1               | - 1             | - 1   | - f              |                 | - 1             | i               | u<br>G          | u Gly           | u Gly           | u Gly           |
|            | بر<br>حب |                                       | · · · · · ·   |            |            | / Glu       | / Glu      |            | / Glu      | / Glu      | <u>B</u>         | 3               |                 | T     |                  |                 |                 | - 1             | 35              | 릉               | a<br>B          | Glu             |
| ·c         | 7        | <u>G</u>                              | Gly           | Gly        | Ala        | Gly         | <u>G</u>   | <u>a</u>   | Gly        | Gly        | <u>G</u>         | <u>.</u>        | <u>ל</u>        |       | 5 6              | <u>ē</u>        | ट्ट             | <u>S</u>        | <u>a</u>        | ਲੁੰ             | ह्य             | <u>G</u>        |
| -          | _        | His                                   | His           | His        | His        | His         | ₽          | 뚮          | 도          | His        | 뚪                | J.S.            | ) <u> </u>      | 2   . | S :              | SE :            | SE              | SE :            | E S             | 욷               | HS<br>H         | HS<br>HS        |
| Acid       | ition    | und 1                                 | and 2         | und 3      | 4 pun      | und 5       | 9 pun      | 7 pun      |            |            | ot pur           | Ind 11          | 12              | 7 0 7 | 2   3            | 5<br>4          | nd 15           | nd 16           | nd 17           | 18<br>18        | 5<br>5<br>5     | 8<br>P          |
| Amino Acid | Position | Compound 1                            | Compound 2    | Compound 3 | Compound 4 | Compound 5  | Compound 6 | Compound 7 | Compound 8 | Compound 9 | Compound 10 HIS  | Compound 11 His | Compound 12 His |       | SILI SI DUNOduno | Compound 14 HIS | Compound 15 HIS | Compound 16 HIS | Compound 17 HIS | Compound 18 HIS | Compound 19 HIS | Compound 20 HIS |
|            | -        |                                       | . , , , ,     | ٠,         | -30        |             |            |            |            |            | 126              | 1               | <u>ب</u>        |       |                  |                 |                 | <u></u>         |                 |                 | $\preceq \bot$  | <u>ٽ</u>        |

Fig. 4A1



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|                        |                |     | -          |            |            |            |            | 7          |            |            |             |             |                 |             |                 |             |             |                 |                 |             |                 |
|------------------------|----------------|-----|------------|------------|------------|------------|------------|------------|------------|------------|-------------|-------------|-----------------|-------------|-----------------|-------------|-------------|-----------------|-----------------|-------------|-----------------|
| 39                     |                |     |            |            |            |            |            |            |            |            |             |             |                 |             |                 |             |             |                 |                 |             |                 |
| 38                     |                |     |            |            |            |            |            | e          |            |            |             |             |                 |             |                 |             |             |                 |                 |             |                 |
| 37                     |                |     |            |            |            |            |            |            |            |            |             |             |                 |             |                 |             |             |                 |                 |             |                 |
| 36                     | . 0            |     |            |            |            | -          |            |            |            |            |             |             |                 |             |                 |             |             |                 |                 |             | *               |
| 35                     |                |     |            |            |            |            |            |            |            |            |             |             |                 | 1:          |                 |             |             | -               |                 |             |                 |
| 34                     |                |     | • .        |            |            | -          |            |            |            | ·          | -           |             |                 | -           |                 |             |             |                 |                 |             | ļ.              |
| 33                     |                |     | . :        |            |            |            |            |            |            |            |             |             |                 |             |                 |             |             |                 |                 |             |                 |
| 32                     |                |     |            |            |            |            |            |            |            |            |             |             |                 | -           |                 |             |             |                 |                 |             |                 |
| 31                     | NHO            | 7   |            |            |            |            |            |            |            |            |             |             |                 |             |                 |             |             | Ĭ               |                 |             |                 |
| 30                     | <u>}</u>       | ŀ   |            |            |            |            |            |            |            |            |             |             |                 |             |                 |             |             |                 |                 |             |                 |
| 29                     | <u>≥</u>       | ١.  | NH2        | NH2        | NH2        | NH2        | NH2        | NFZ        | NH2        | NH2        | NH2         | NH2         | NF2             | NH2         | NH2             | NH2         | NF2         | NH2             | NH2             | NH2         | NFZ             |
| 28                     | Acn            |     | Asn        | Asn        | Asn        |            | Asn NH2    | Asn        |            | Asn        | Asn         | Asn         | Asn             | Asn         | Asn             | 1           | Asn         | Asn             |                 | Asn         | ļ               |
| 27                     | /8             | - 1 | Lys         | Lys         | Lys             | Lys         | Lys             | Lys Asn     | Lys Asn NH2 | Lys             | Lys             | Lys         | Lys Asn         |
| 26                     | <u>a</u>       |     | EG<br>FG   | Leu        | Leu        | Leu        |            | Leu .      |            |            |             | neŋ         | Leu             | Leu         | Fen             | Leu         | ren         | Leu             | ren             | ren         | ren             |
| 25                     | T <sub>C</sub> | - 1 | <u>e</u>   | Phe        | Phe Leu    | Glu Phe    | Phe Leu     | Phe         | Phe             | Phe         | Phe             | Phe         | Phe         | Phe             | Phe             | Phe         | Ala             |
| 24                     | - E            | 3 0 | n<br>E     | Glu        | Olu        | elu        |            |            | Olu        |            |             |             | ļ               | nıg         | Glu             | Glu         | Glu         | Glu             | Glu             | Ala         | Glu             |
| 23                     | اع ا           | 2 - | <u>=</u>   | <u>lle</u> | Ile        | Ilè        | Ile        | Ile        | Ile        | Ile        | Ile         | Ile         | Ile             | Ile         | ]le             | Ile         | Ile         | Ile .           | Ile             | Ile         | Ile             |
| 22                     | Phe            |     | rne<br>E   | 윤          | Phe         | Phe         | Phe             | Phe         | Phe             | Phe         | Phe         | Phe             | Phe             | Phe         | Phe             |
| 21                     | ē              | - 1 | e          | ren        | Leu        | ren        | Leu        | ren        | ren        | Leu        | ren         | Leu         |                 | Leu         |                 | Leu         | ə           |                 |                 | Fe          | - 4             |
| Amino Acid<br>Position | Compound 1     | _   | Compound 2 | Compound 3 | Compound 4 | Compound 5 | Compound 6 | Compound 7 | Compound 8 | Compound 9 | Compound 10 | Compound 11 | Compound 12 Leu | Compound 13 | Compound 14 Leu | Compound 15 | Compound 16 | Compound 17 Leu | Compound 18 Ala | Compound 19 | Compound 20 Leu |

Fig. 4A2



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| 10   10   10   10   10   10   10   10  |         |          | T :-       | 1        | J ==          | J -         | J =        | <del></del> |            |          | <del></del> | 7        |          | 1=       | <del></del> |          | J =      | J _         | · -           | <del></del> |          |          | _       |
|--|---------|----------|------------|----------|---------------|-------------|------------|-------------|------------|----------|-------------|----------|----------|----------|-------------|----------|----------|-------------|---------------|-------------|----------|----------|---------|
| Amino Acid 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 Compound 21 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Vompound 22 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Vompound 22 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Vompound 22 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Vompound 23 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Vompound 24 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Vompound 25 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Vompound 26 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Vompound 27 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Vompound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Vompound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Vompound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Vompound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Vompound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Vompound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Vompound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Vompound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Glu Ala Vompound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Vompound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Glu Ala Vompound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Glu Ala Vompound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Glu Ala Vompound 49 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Glu Glu His Dompound 49 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Glu Leu Glu Glu Glu Glu Glu Glu Glu Glu Glu Gl             |         | 22       | Arg        | Y V      | Arg.          | A P         | Aro        | Ard         | Arg        | Ard      | Arg         | Arg      | Arg      | Arg      | Ard         | Ara      | Arg      | Ard         | Ard           | Ard         | Arg      | Ard      | Ara     |
| Amino Acid 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17  Compound 22 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Leu Glu Glu Glu Glu Compound 22 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Leu Glu Glu Glu Glu Compound 22 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Compound 23 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Compound 25 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Compound 25 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Compound 25 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Compound 25 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Compound 25 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Compound 25 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Compound 25 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Glu Compound 25 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Glu Compound 35 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Glu Compound 35 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Glu Compound 35 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Compound 35 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Compound 35 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Glu Glu Glu Glu Compound 35 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Gu Glu Glu Glu Glu Glu Glu Glu Glu Glu   | ;       | <u> </u> | \Sa<br>\Sa | \S       | \S            | R           | E          | \S          | a<br>S     | \ag      | Val         | Val      | Val      | Val      | Val         | Val      | Val.     | \S          | Val           | Sal         | Sal      | \sqr     | \S      |
| Amino Acid 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17  Compound 22 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Leu Giu Glu Glu Compound 22 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Leu Giu Glu Glu Compound 22 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Glu Compound 22 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Glu Compound 22 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Glu Compound 22 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Glu Compound 22 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Glu Compound 22 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Glu Compound 22 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Compound 23 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Compound 23 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Compound 23 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Compound 33 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Compound 35 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Compound 35 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Compound 35 His Giy Glu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Compound 35 His Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Compound 35 His Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Giu Compound 35 His Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Giu Giu Giu Giu Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Giu Giu Giu Giu Compound 41 His Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Giu Giu Giu Giu Compound 41 His Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Giu Giu Giu Giu Giu Compound 41 His Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Giu Giu Giu Giu Giu Giu Compound 41 His Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Giu Giu Giu Giu Giu Giu Compound 41 His Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Giu Giu Giu  | ç       | <u> </u> | Ala        | Ala      | Ala           | Ala         | Ala        | Ala         | Ala        | Ala      | Ala         | Ala      | Ala      | Ala      | Ala         | Ala      | Ala      | Ala         | Ala           | Ala         | Ala      | Ala      | Ala     |
| Amino Acid 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 Compound 22 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Compound 22 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Compound 23 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 24 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 25 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 26 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 27 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Compound 48 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Compound 48 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Compound 48 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Compound 48 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Compound 48 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Compound 48 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Glu Cu Glu Glu Gly Thr Phe Thr Ser Asp Leu S | ţ       | <b>=</b> | ng<br>B    | Glu      | JIB<br>B      | 3           | Glu        | Glu         | Gle        | Glu      | Glu         | Glu      | Glu      | Glu      | 1           | 1        | GIS.     | nlg<br>U    | 195           |             | -        | 1        | 1       |
| Amino Acid 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 15 Compound 21 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Compound 22 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Compound 22 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Compound 24 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 39 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 39 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 39 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 39 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Compound 39 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Compound 49 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Compound 41 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Compound 41 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Glu Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Glu Glu Gly Thr Phe  |         | <u> </u> | 7          |          | T             |             | 1          |             | 1          |          | 1           | 1        | Į        | i .      |             | 1        |          |             | 1             |             |          | 1        |         |
| Amino Acid 1 2 3 4 5 6 7 8 9 10 11 12 13 14 14 5 Position  Compound 21 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 22 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 22 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 23 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 23 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Compound 31 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Compound 31 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Compound 40 Hi  | Ų       | <u>.</u> | 1          |          | T             | T           |            | I           |            | 1        |             |          |          | 1        |             |          |          |             | T             |             |          |          |         |
| Amino Acid 1 2 3 4 5 6 7 8 9 10 11 12 13 Compound 21 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 22 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 23 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 23 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 25 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 27 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 29 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 31 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 31 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 31 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Compound 40 His Gly G | -       | <u>+</u> |            | 1        | T             | 1           | 1 .        | 1           | i          |          |             |          | •        |          | 1           | 1        |          |             | _             | F           | 1        | _        |         |
| Amilio Acid         1         2         3         4         5         6         7         8         9         10         11         12           Position         Compound 21 His         Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser         Lys           Compound 22 His         Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser         Lys           Compound 22 His         Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser         Lys           Compound 22 His         Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser         Lys           Compound 22 His         Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser         Lys           Compound 28 His         Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser         Lys           Compound 32 His  | 5       | 2 .      | 1          | 1        | 1             |             | _          | 1           |            |          |             |          | 1        | 1        |             |          | -        |             | 등             |             | iii.     | -        | 1       |
| Amilio Acid         1         2         3         4         5         6         7         8         9         10         11           Position         Compound 22 His         Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser           Compound 22 His         Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser           Compound 22 His         Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser           Compound 22 His         Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser           Compound 22 His         Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser           Compound 23 His         Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser           Compound 30 His         Gly         Glu         Gly         Thr         Phe         Thr         Ser <td>5</td> <td>7</td> <td></td> <td></td> <td>T</td> <td></td> <td>T</td> <td></td> <td></td> <td>- 11</td> <td>1</td> <td>i</td> <td>ľ</td> <td></td> <td>1</td> <td></td> <td></td> <td></td> <td></td> <td>i</td> <td>ı</td> <td></td> <td>1</td>  | 5       | 7        |            |          | T             |             | T          |             |            | - 11     | 1           | i        | ľ        |          | 1           |          |          |             |               | i           | ı        |          | 1       |
| Amilio Acid 1 2 3 4 5 6 7 8 9 10  Compound 21 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 22 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 23 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 24 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 29 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 31 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 31 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 32 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 33 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 35 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 35 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 35 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 36 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 39 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 39 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 39 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Compound 40 His Gly Glu Gly Thr Phe  | =       | <u>,</u> | <b></b>    |          | 1             |             |            |             |            |          |             |          |          |          |             |          |          |             |               |             |          |          |         |
| Amino Acid 1 2 3 4 5 6 7 8 9  Compound 21 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 22 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 22 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 23 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 24 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 25 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 28 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 39 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 31 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 31 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 32 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 38 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 39 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 39 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 39 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 39 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp Compound 40 His Gly Glu Gly Thr Phe Thr Ser Asp  | Ç       | 2        |            | 1        |               |             |            |             |            |          |             |          | 1        | ٠.       |             | , ,      |          |             | i             | ł           |          |          |         |
| Amino Acid 1 2 3 4 5 6 7 8  Compound 21 His Gly Glu Gly Thr Phe Thr Ser Compound 22 His Gly Glu Gly Thr Phe Thr Ser Compound 23 His Gly Glu Gly Thr Phe Thr Ser Compound 24 His Gly Glu Gly Thr Phe Thr Ser Compound 25 His Gly Glu Gly Thr Phe Thr Ser Compound 25 His Gly Glu Gly Thr Phe Thr Ser Compound 26 His Gly Glu Gly Thr Phe Thr Ser Compound 27 His Gly Glu Gly Thr Phe Thr Ser Compound 31 His Gly Glu Gly Thr Phe Thr Ser Compound 31 His Gly Glu Gly Thr Phe Thr Ser Compound 32 His Gly Glu Gly Thr Phe Thr Ser Compound 32 His Gly Glu Gly Thr Phe Thr Ser Compound 33 His Gly Glu Gly Thr Phe Thr Ser Compound 34 His Gly Glu Gly Thr Phe Thr Ser Compound 36 His Gly Glu Gly Thr Phe Thr Ser Compound 36 His Gly Glu Gly Thr Phe Thr Ser Compound 36 His Gly Glu Gly Thr Phe Thr Ser Compound 36 His Gly Glu Gly Thr Phe Thr Ser Compound 38 His Gly Glu Gly Thr Phe Thr Ser Compound 38 His Gly Glu Gly Thr Phe Thr Ser Compound 38 His Gly Glu Gly Thr Phe Thr Ser Compound 38 His Gly Glu Gly Thr Phe Thr Ser Compound 38 His Gly Glu Gly Thr Phe Thr Ser Compound 40 His Gly Glu Gly Thr Phe Thr Ser Compound 40 His Gly Glu Gly Thr Phe Thr Ser  |         |          | l ds/      | \sp [    | \sp [         | \sp [       | l ds/      |             |            |          |             |          | sp [     |          |             |          |          |             |               |             |          |          |         |
| Amino Acid 1 2 3 4 5 6 7  Position  Compound 21 His Gly Glu Gly Thr Phe Thr Compound 22 His Gly Glu Gly Thr Phe Thr Compound 22 His Gly Glu Gly Thr Phe Thr Compound 24 His Gly Glu Gly Thr Phe Thr Compound 28 His Gly Glu Gly Thr Phe Thr Compound 28 His Gly Glu Gly Thr Phe Thr Compound 28 His Gly Glu Gly Thr Phe Thr Compound 29 His Gly Glu Gly Thr Phe Thr Compound 39 His Gly Glu Gly Thr Phe Thr Compound 31 His Gly Glu Gly Thr Phe Thr Compound 34 His Gly Glu Gly Thr Phe Thr Compound 35 His Gly Glu Gly Thr Phe Thr Compound 36 His Gly Glu Gly Thr Phe Thr Compound 36 His Gly Glu Gly Thr Phe Thr Compound 37 His Gly Glu Gly Thr Phe Thr Compound 37 His Gly Glu Gly Thr Phe Thr Compound 38 His Gly Glu Gly Thr Phe Thr Compound 39 His Gly Glu Gly Thr Phe Thr Compound 39 His Gly Glu Gly Thr Phe Thr Compound 39 His Gly Glu Gly Thr Phe Thr Compound 39 His Gly Glu Gly Thr Phe Thr Compound 40 His Gly Glu Gly Thr Phe Thr Compound 40 His Gly Glu Gly Thr Phe Thr Compound 40 His Gly Glu Gly Thr Phe Thr  |         |          |            | er       | θľ            |             |            |             |            |          |             |          |          |          |             |          | - 1      | ы           | , i           |             |          |          |         |
| Amino Acid         1         2         3         4         5         6           Position         Compound 21 His         Gly         Glu         Gly         Thr         Phe           Compound 22 His         Gly         Glu         Gly         Thr         Phe           Compound 25 His         Gly         Glu         Gly         Thr         Phe           Compound 26 His         Gly         Glu         Gly         Thr         Phe           Compound 27 His         Gly         Glu         Gly         Thr         Phe           Compound 28 His         Gly         Glu         Gly         Thr         Phe           Compound 31 His         Gly         Glu         Gly         Thr         Phe           Compound 38 His         Gly         Glu         Gly         Thr         Phe           Compound 38 His         Gly         Glu         Gly         Thr  |         |          |            |          |               |             |            |             |            |          |             |          |          |          |             | - 1      |          |             |               |             |          |          |         |
| Amino Acid         1         2         3         4         5           Position         Compound 21 His         Gly         Gly         Gly         Thr           Compound 22 His         Gly         Gly         Gly         Thr           Compound 22 His         Gly         Gly         Gly         Thr           Compound 24 His         Gly         Gly         Gly         Thr           Compound 25 His         Gly         Gly         Gly         Thr           Compound 27 His         Gly         Gly         Gly         Thr           Compound 27 His         Gly         Gly         Gly         Thr           Compound 28 His         Gly         Gly         Gly         Thr           Compound 31 His         Gly         Gly         Gly         Thr           Compound 32 His         Gly         Glu         Gly         Thr           Compound 34 His         Gly         Glu         Gly         Thr           Compound 35 His         Gly         Glu         Gly         Thr           Compound 36 His         Gly         Glu         Gly         Thr           Compound 37 His         Gly         Glu         Gly  |         |          |            |          |               |             |            | _           |            |          |             |          |          |          |             |          | <u> </u> |             |               |             |          |          |         |
| Amino Acid 1 2 3 4  Position  Compound 21 His Gly Glu Gly Compound 22 His Gly Glu Gly Compound 23 His Gly Glu Gly Compound 24 His Gly Glu Gly Compound 25 His Gly Glu Gly Compound 26 His Gly Glu Gly Compound 27 His Gly Glu Gly Compound 28 His Gly Glu Gly Compound 29 His Gly Glu Gly Compound 30 His Gly Glu Gly Compound 31 His Gly Glu Gly Compound 32 His Gly Glu Gly Compound 34 His Gly Glu Gly Compound 37 His Gly Glu Gly Compound 37 His Gly Glu Gly Compound 37 His Gly Glu Gly Compound 38 His Gly Glu Gly Compound 38 His Gly Glu Gly Compound 38 His Gly Glu Gly Compound 39 His Gly Glu Gly Compound 41 His Gly Glu Gly Compound 41 His Gly Glu Gly Compound 41 His Gly Glu Gly  |         | ` .      |            |          |               |             |            |             | i          |          | $\neg \tau$ |          |          |          | :           |          |          |             |               |             |          |          | 느       |
| Amino Acid 1 2 3 Position Compound 21 His Gly Glu Compound 22 His Gly Glu Compound 22 His Gly Glu Compound 24 His Gly Glu Compound 25 His Gly Glu Compound 26 His Gly Glu Compound 27 His Gly Glu Compound 28 His Gly Glu Compound 39 His Gly Glu Compound 30 His Gly Glu Compound 31 His Gly Glu Compound 32 His Gly Glu Compound 32 His Gly Glu Compound 34 His Gly Glu Compound 36 His Gly Glu Compound 37 His Gly Glu Compound 36 His Gly Glu Compound 37 His Gly Glu Compound 38 His Gly Glu Compound 38 His Gly Glu Compound 38 His Gly Glu Compound 39 His Gly Glu Compound 31 His Gly Glu Compound 41 His Gly Glu  | "       | <b>'</b> |            |          |               |             |            |             |            |          |             |          |          |          |             |          | · -      |             | <del>  </del> |             |          |          | 1       |
| Amino Acid 1 2 Position Compound 21 His Gly Compound 22 His Gly Compound 24 His Gly Compound 24 His Gly Compound 25 His Gly Compound 26 His Gly Compound 27 His Gly Compound 30 His Gly Compound 30 His Gly Compound 31 His Gly Compound 32 His Gly Compound 32 His Gly Compound 34 His Gly Compound 36 His Gly Compound 37 His Gly Compound 37 His Gly Compound 37 His Gly Compound 37 His Gly Compound 38 HIS Gly Compound 36 HIS Gly Compound 37 His Gly Compound 37 His Gly Compound 38 HIS Gly Compound 41 HIS Gly  | 7       | -        |            | - 1      |               |             |            |             | - 1        | - 1      | - 1         | 1        | 1        | - 1      |             |          | 9        | 9           | <u>ဗ</u> ု    | 9           | <u>ත</u> | 5        | 힐       |
| Amino Acid Position Compound 21 His Compound 22 His Compound 23 His Compound 24 His Compound 25 His Compound 26 His Compound 27 His Compound 28 His Compound 30 His Compound 30 His Compound 31 His Compound 32 His Compound 33 His Compound 34 His Compound 36 His Compound 37 His Compound 36 His Compound 37 His  | ۲.      |          |            | <u>ত</u> | - 1           | - 1         | - 1        |             |            |          |             |          |          |          | 1           | - 1      | 1.0      | - 1         | 1             | - 1         | - 1      | - 1      |         |
|  | 2       | 1        | <u>g</u>   | - 1      | ह्य           | <u>ड</u>    | <u>a</u>   | ह           | <u>ड</u> े | <u>@</u> | ट्ट         | <u>@</u> | <u>8</u> | <u>@</u> | <u>8</u>    | <u>ම</u> | <u>छ</u> | ले          | ਲੁ            | ह्य         | ह्य      | <u>8</u> | ह्य     |
|  | _       | -        | H:S        | His      | E<br>Figure 1 | 五<br>子<br>子 | His<br>His | SHS         | His<br>His | 도<br>문   | SH S        | S<br>E   | SE .     | HS       | S HS        | SE I     | E. Fis   | SH S        | E.            | 읦           | HIS      | 위<br>문   | 읦       |
|  | no Acio | sition   | ound 2     | ound 2   | S pund 5      | ound 2      | ound 2     | ound 26     | ound 2     | ound 25  | ound 25     | ound 3(  | ound 3   | ound 3%  | ound 3:     | % puno   | ound 35  | ound 36     | ound 37       | 3E puno     | ound 35  | ound 40  | ound 41 |
|  | Amin    | å        | Comp       | Somb     | g<br>B        | Comp        | Somb       | S           | Semb       | S        |             |          | Comp     | S        | S           | Comp     | 8        | ğ<br>B<br>S | Comp          | Comp        | d Log    | Somb     | Сощр    |

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|------------------------|-------------|-------------|-------------|-------------|-----------------|-------------|-------------|-------------|-----------------|-----------------|-------------|-----------------|-------------|-----------------|-----------------|-------------|-------------|-------------|-----------------|-----------------|-----------------|
|                        |             |             |             |             |                 |             |             |             |                 |                 |             |                 |             |                 |                 |             |             |             |                 |                 |                 |
| 39                     |             |             |             | NH2         | NH2             |             |             |             |                 |                 |             |                 |             |                 |                 |             |             |             |                 |                 |                 |
| 38                     | 1           |             | -           | Pro         | T               | NH2         | NH2         | :           |                 |                 |             |                 |             |                 |                 |             |             |             |                 |                 |                 |
| 37                     |             |             |             | Pro         | Pro             | Pro         | Pro         | NH2         | NH2             |                 |             |                 |             |                 |                 |             |             |             |                 |                 | :               |
| 36                     |             |             |             | Pro         | Pro             | Pro         | Pro         | Pro         | Pro             | NHZ             | NH2         |                 |             |                 |                 |             |             |             |                 |                 | · ·             |
| 35                     |             |             |             | Ala         | Ala             | Ala         | Ala         | Ala         | Ala             | Ala             | Ala         | NH2             | 꾪           |                 |                 |             |             |             |                 |                 | ν.              |
| 34                     |             |             |             | Gly         | Gly             | Gly         | G<br>G      | <u>ਰ</u>    | G<br>Sign       | Gly ,           | Gly.        | G<br>G          | G<br>G      | NH2             | NF2             |             |             |             |                 |                 | . '             |
| 33                     |             |             |             | Ser         | Ser             | Ser         | Ser         | Ser         | Ser             | Ser             | Ser         | Ser             | Ser         | Ser             | Ser             | NH2         | NH2         |             |                 |                 | *.              |
| 32                     |             |             |             | Ser         | Ser             | Ser         | Ser         | Ser         | Ser             | Ser             | Ser         |                 | Ser         | Ser             | Ser             | Ser         | Ser         | NH2         | NH2             |                 |                 |
| 31                     |             | ļ           |             | Pro         | Pro (           | Pro (       | Pro         | Pro         | Pro             |                 | Pro         |                 |             | Pro             | 1               | Pro         | Pro         | Pro         | Pro             | NH2             |                 |
| 30                     |             |             |             | Gly         | Gly             |             | Gis         | Gly         | Gly             | g               | Gly         | T               | G<br>S      |                 | Gly             | Gly         | G<br>G      | Gi          | G<br>G          | Gly             | NH2             |
| 29                     | NH2         | NH2         | NH2         | Gly         | Gly             | Gly         | Gly         | Gly         | Gly             | G<br>Š          | Gly         | Gly             | Gly         | S<br>S          | Gly             | Gly         | S<br>S      | G<br>Sign   | Gly             | Gly             | Gly             |
| 28                     | Asn         | Asn         | Ala         | Asn (       | Asn (           | Asn         | Asn         | Asn (       | Asn             | Asn             | Asn         | Asn             | Asn         | Asn             |                 |             | _           | 1 '         | Asn             | Asn             | Asn             |
| 27                     | Lys         | Ala /       | Lys /       | Lys /       | Lys /           | rys         | rys /       | Lys ,       | rys 🚶           | rys.            | rys '       | Lys             | ' s⁄ı¬      | rys ,           | rys             | Lys         | rys.        | Lys         | Lys             | Lys ,           | Lys             |
| 26                     | Ala         | Leu         | Leu         | ren         | ne7             | ren         | ren         | ne-T        | nen             | ren             | ren         | ren             | ren         | Leu             | l uəl           | ren         | Leu<br>Leu  | Lei         | ren             | ren             | <br> <br> <br>  |
| 25                     | Phe /       | Phe         | Phe         | Trp         | Phe             | Trp         | Phe         | l dil       | eya             |                 |             |                 | Phe         | Trp             | Phe             | Trp         | Phe         | Tr<br>dr    | Phe             | Phe             | Tro             |
| 24                     | Gen         |             | Glu         | .   JIB     |                 |             |             | Ng          | Glu             |                 | Glu         |                 |             |                 |                 | Olu         |             | Je          | Glu             | Glu             |                 |
| 23                     | lle         | )<br>e][    | ) ell       | ) eji       | ) ell           | ) ell       | lle (       | )  all      | )<br> <br> <br> | ) eli           | )<br>ell    | lle (           | ][e         | ]le (           | Ile             | ]le         | ) eji       | ][e         | lle (           | ]]e             | ]]e             |
| 22                     | Phe 1       | Phe 1       | Phe 1       | Phe         | Phe I           | Phe         | Phe         | Phe 1       | Phe 1           | Phe 1           | Phe         | Phe             | Phe         | Phe 1           | Phe             | Phe         | Phe 1       | Phe         |                 | Phe ]           | Phe             |
| 21                     | Leu         | ne l        | Leu         | Leu l       |                 | ne-         | Leu         | Leu I       |                 |                 | en l        |                 | le.         |                 |                 | a-          | l na-       | ren l       | ne-             | ne              |                 |
| Amino Acid<br>Position | Compound 21 | Compound 22 | Compound 23 | Compound 24 | Compound 25 Leu | Compound 26 | Compound 27 | Compound 28 | Compound 29 LeU | Compound 30 Leu | Compound 31 | Compound 32 Leu | Compound 33 | Compound 34 Leu | Compound 35 Leu | Compound 36 | Compound 37 | Compound 38 | Compound 39 Leu | Compound 40 Leu | Compound 41 Leu |

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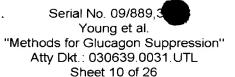
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|--------|---|---|--|---|---|--|--|--|--|---|---|---|---|---|--|--|--|--|--|
| Arg    | Arg   | Arg   | Arg  | Arg   | Arg   | Arg  | Arg  | Arg  | Arg  | Arg   | Arg   | Arg   | Arg   | Arg   | Arg  | Arg  | Arg  | Arg  | Arg  |
| Val    | Val   | Val   | Val  | Val   | Val   | Val  | Val  | Val  | Val  | Val   | Val   | Val   | Val   | Val   | Val  | Val  | Val  | Val  | Val  |
| Ala    | Ala   | Ala   | Ala  | Ala   | Ala   | Ala  | Ala  | Ala  | Ala  | Ala   | Ala   | Ala   | Ala   | Ala   | Ala  | Ala  | Ala  | Ala  | Ala  |
|        | glu   |   | glu  | gla   | 1   | glu  | glu  | (4)  |  | Glu   | $\Gamma$  |   | Glu   |   | Glu  | Glu  | Glu  | Glu  | Glu  |
|        |   |   |  |   |   |  |  |  |  |   |   |   |   | -   |  |  |  |  | Glu  |
|        |   |   |  | 1   |   |  |  |  | 1  |   |   |   | i   |   | 3lu ·  |  |  |  | Glu  |
|        |   |   |  |   |   |  |  |  | 1  |   |   |   |   |   | ı  |  |  |  | Met (  |
|        | T   |   |  |   |   |  |  |  |  |   |   |   |   |   |  |  | <del></del>  |  | Gln  |
|        |   |   |  |   |   |  |  |  |  |   |   |   |   |   |  |  |  |  | Lys (  |
| 1      |   |   |  |   |   |  |  | 1  | -  |   |   |   |   |   |  |  |  |  | Ser L  |
|        |   |   |  |   |   |  |  |  |  |   |   |   | GlyS  |   |  |  | a  | В  | Ala S  |
| 1-     |   |   |  | _   |   |  |  |  | <u> </u>   | _   |   |   |   |   |  |  |  |  | Asp A  |
| 1.     | · ·   |   |  |   |   |  |  |  |  |   |   |   |   |   |  |  |  |  |  |
| S      | တ   | S   | S  | S   |   |  |  |  |  |   |   |   |   | S   |  |  | S  |  | r Ser  |
| +-     | <del>                                     </del>                    |   |  | _   |   | _  |  |  | Th   | e Se  |   |   |   |   |  |  |  |  | e Thr  |
|        |   |   | -  |   |   |  |  |  |  |   |   |   |   |   |  |  |  |  | Phe  |
| Thr    | Thr   | Thr   | Thr  |   | Thr   | Thr  | <del> </del>   | Thr  | Thr  | Thr   | Thr   | Thr   | Ė   |   | Th   | Thr  | Thr  | Thr  | Thr  |
| G      | <u>G</u>  | Gly   | Gly  | Gly   | Gly   | Gly  | Gly  | Gly  | Gly  | Gly   | Gly   | Gly   | <u>ල</u>  | ਲੁ  | <u>G</u>   | Gly  | Gly  | Gly  | Gly  |
| Glu    | Glu   | Glu   | Glu  | Glu   | Glu   | Glu  | Glu  | Asp  | Glu  | gln   | Glu   | Glu   | <u>B</u>  | <u></u>   | <u>B</u>   | Glu  | Glu  | Glu  | 픙  |
| GÌ     | Gly   | Gly   | Gly  | Gly   | Gly   | Gly  | Gly  | Gly  | Gly  | Gly   | <u>G</u>  | <u>aly</u>  | <u>a</u>  | <u>S</u>  | <u>G</u>   | Gly  | Gly  | <u>G</u>   | ਲੇ   |
| His    | His   | His   | His  | His   | HIS   | His  | Arg  | His  | HIS  | His   | His   | His   | His   | His   | HIS  | His  | HIS  | HIS  | 웊  |
| und 42 | und 43  | und 44  | und 45   | und 46  | und 47  | und 48   | und 49   | og pund  | ound 51  | ound 52   | ound 53   | ound 54   | ound 55   | ound 56   | 75 pund  | ound 58  | ound 59  | 09 punc  | Compound 61 HIS  |
| Compo  | Сотрс   | Сотрс   | Сотрс  | Сотрс   | Сотрс   | Сотрс  | Сотрс  | Сотрс  | Сотрс  | Сотрс   | Сотрс   | Сотрс   | Сотрс   | Сотрс   | Сотрс  | Сотрс  | Сотрс  | Сощр   | Compa  |
|        | Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val | Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ha Val<br>Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val | Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ha Val<br>Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val<br>Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val | Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val | Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ha Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ha Val Gly Glu Gly Thr Phe Thr Ser Asp 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Glu Glu Ha Val Gly Glu Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ha Val Gly Glu Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Glu Ala Val | Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ha Val Gly Glu Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln 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Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Ser Thr Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ha Na Val Gly Glu Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met Glu Glu Glu Ha Na Val Gly Glu Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met Glu Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met Glu Glu Glu Glu Ala Val Gly Glu Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met Glu Glu Glu Glu Ala Val | Gly Glu Gly Thr 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Ser Lys Gln Met Glu Glu Glu Ha Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ha Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ha Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ha Val Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ha Val Gly Gly Gly Gly Gly Gly Gly Gly Gly Gl | Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Ala Val Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Giu Ala Val Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Ala Val Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Ala Val Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Ala Val Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Ala Val Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Ala Val Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu Giu Ala Val Giy Giu Giy Thr Phe Thr Ser Asp Leu Ser Lys Gin Met Giu Giu 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|                        |             |             |             | •           |                     |             |             |             |             | •               |             |             |             |                 |             |             |                 | اب.         | ,<br>       |                 |
|------------------------|-------------|-------------|-------------|-------------|---------------------|-------------|-------------|-------------|-------------|-----------------|-------------|-------------|-------------|-----------------|-------------|-------------|-----------------|-------------|-------------|-----------------|
| MIN G                  |             |             |             |             |                     |             |             |             |             |                 |             |             |             |                 |             |             | 1               |             |             |                 |
| 39                     |             | NH2         | NH2         |             |                     |             | ,           |             |             |                 |             |             |             |                 |             |             |                 |             |             |                 |
| 38                     |             | tPro        | tPro        | NH2         | NFS                 | NH2         |             |             |             |                 |             |             |             |                 |             |             |                 |             |             | SH2             |
| 37                     |             | tPro        | tPro        | Pro         | 1                   | h<br>Dro    | 꽃           |             |             |                 |             |             |             |                 |             |             |                 |             |             | hPro            |
| 36                     |             | tPro        | tPro        | Pro         | Nme                 | hPro        | hPro NH2    | NH2         |             |                 | -,          |             |             |                 |             |             |                 |             |             | hPro hPro NH2   |
| 35                     |             | Ala         | Ala         | Ala         | Ala                 | Ala         | Ala         | Ala         |             |                 |             |             |             |                 |             |             |                 |             |             | Ala             |
| 34                     |             | g           | G<br>G      | <u>S</u>    | हि                  | Gl          | GIÝ.        | Gl          |             |                 |             |             |             |                 |             |             | ;               | NH2         |             | 3               |
| 33                     |             | Ser         | Ser         | Ser         | Ser                 | Ser         | Ser         | Ser         |             |                 |             |             |             |                 |             |             |                 | Ser         |             | Ser             |
| 32                     |             | Ser         | Ser Ser     | Ser         | Ser                 | Ser         | Ser         | Ser         |             | ,               |             |             |             |                 |             |             |                 | Ser         |             |                 |
| 31                     |             | tPro        | Pro         | Nme Ser     | Nme                 | hPro Ser    | hPro        | Pro         | SHN<br>NF2  |                 |             |             |             |                 |             |             |                 | Pro         | 1           | hPro Ser        |
| 30                     | 꽃           | Gly         | Gly         | Gly         | g<br>g              | Gly         | ල්          | al<br>S     | Glý         |                 |             |             |             |                 |             |             |                 | Gly         | NH2         | Ğ               |
| 29                     | <u>B</u>    | Gly         | Gly         | Gly         | g                   | Gly         | <u>G</u>    | GÌ          | <u>a</u>    | NH2             | NF2         | N<br>H<br>S | NHZ         | NH2             | NHZ         | NH2         | NH2             | G<br>G      | Glý         | <u>S</u>        |
| 58                     | Asn         | Asn         | Asn         | Asn         | Asn                 | Asn         | Asn         | Asn         | Asn         | Asn             | Asn         | Asn         | Asn         | Asn             | Asn         | Asn         | Asn             | Asn         | Asn         | Asn             |
| 27                     | Lys         | Lys         | Lys         | Lys         | Lys                 | Lys         | Lys         | Lys         | Lys         | Lys             | Lys         | Lys         | Lys         | Lys             | Lys         | Lys         | Lys             | Lys         | Lys         | Lys             |
| 26                     | ren         | Leu         | Leu         | Leu         | ren ·               | Leu         | ren         | E<br>E      | <u>B</u>    | Leu             | Leu         | ne<br>Ten   | <u></u>     | ren             | ren         | ren         | Leu             | ren         | Leu         | Leu             |
| 25                     | Phe         | <u>a</u>    | <u>L</u>    | Trp         | Trp                 | Trp         | Trp         | Trp         | Trp         | Phe             | Trp         | Trp         | Trp         | Phe             | Phe         | Trp         | Phe             | Phe         | Trp         | Trp             |
| 24                     | ළ           | e<br>e      | <u></u>     | ВП          | ЭB                  | 믮           | Glu         | Glu         | Glu         | Glu             | nıg         | ng          | Olu         | Glu             | Glu         | OE<br>OE    | Asp             | Glu         | glu ,       | <u> </u>        |
| 23                     | ile<br>Ile  | <u>e</u>    | e<br>E      | <u>l</u> e  | <u>e</u>            | Ile         | Ile         | Ile         | əll         | e]]             | əll         | a][e        | Ile .       | Ile             | ·           | tBug        | Ile             | Ile         | Ile         | <u>e</u>        |
| 22                     | Phe         | Phe         | Phe         | Phe         |                     | Phe         | Phe         | Phe         | Phe         | Phe             | Phe         | Phe         | Phe         | Phe             | naph Ile    | Phe         | Phe             | Phe         | Phe         | Phe             |
| 21                     | Fen         | <u>E</u>    | <b>E</b>    | 핆           | Leu                 | E E         | E E         | E           | Fen         | - 1             | Leu         | Leu         | Leu         | - 1             | -en         | Leu         |                 | E           | Fer         |                 |
| Amino Acid<br>Position | Compound 42 | Compound 43 | Compound 44 | Compound 45 | Compound 46 Leu Phe | Compound 47 | Campound 48 | Compound 49 | Compound 50 | Compound 51 Leu | Compound 52 | Compound 53 | Compound 54 | Compound 55 Leu | Compound 56 | Compound 57 | Compound 58 Leu | Compound 59 | Compound 60 | Compound 61 Leu |



Compound No. 4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys-NH<sup>E</sup>octanoyl Asn-NH<sub>2</sub> 62

4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys-NH<sup>E</sup>octanoyl Asn-NH<sub>2</sub> 63

4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys-NH<sup>E</sup>octanoyl Asn Gly Gly-NH<sub>2</sub> 64 10/26

4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val 65

Arg Leu Phe Ile Glu Phe Leu Lys-NH<sup>E</sup>octanoyl Asn Gly Gly-NH<sub>2</sub>

4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu 99

Phe Ile Glu Trp Leu Asn Lys-NH $^{
m E}$ octanoyl-NH $_2$ 

Fig. 4C



Compound No. 4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Asn Lys-NH $^{
m E}$ octanoyl-NH $_2$ **6**7

4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu

Phe Ile Glu Trp Leu Asn Lys-NH $^{
m E}$ octanoyl Gly Gly-NH $_2$ 

4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu

Phe Ile Glu Phe Leu Asn Lys-NH $^{
m E}$ octanoyl Gly Gly-NH $_2$ 

## Fig. 4L

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| 20                     | Ard             | Ara             | Aro             | Aro             | Ard             | Ara             | Ard             | Ard             | Ard             | Ard             | Arg        | Ard             | Ara             | Ara             | Ara             | Ard             | Aro             | Ara             | Ard             | Ard             |
|------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| ·                      |                 |                 |                 |                 |                 |                 |                 |                 | 1               |                 | T -        |                 | X               |                 |                 | Ţ               | X               | V               | : ▼             |                 |
| 19                     | Sa              | Va              | 2               | S               | S S             | \Z              | Sal             | Sa              | Val             | \alpha          | Val        | Val             | Sa              | \Za             | \Sal            | Va              | \S              | Za/             | Sal             | \S              |
| 138                    | Ala             | Ala        | Ala             | Ala             | Ala             | Ala             | Ala             | Ala             | Ala             | Ala             | Ala             |
| 17                     | Glu             | <u> </u>        |                 | 000             | 35              | Glu             | a<br>B<br>B     | 99              | <u></u>         | Glu             | Glu        | Glu             | n<br>B          | nl9             | ng<br>B         | n<br>B          | Glu             | Glu             | Olu<br>Glu      | Glu             |
| 16                     | 195             | Glu             | Glu             | Glu             | all<br>G        | Glu             | Glu             | Glu             | Glu             | Glu             | Glu        | Glu             | Glu             | Glu             | Glu             | Glu             | Glu             | Glu             |                 | Glu             |
| 15                     | nlb             | Glu             | Glu        | Glu             | Glu             | Glu             | Glu             | Glu             | Glu             | Gli             |                 | Glu             |
| 14                     | Leu             | Leu             |                 | Leu             | Met             | Met             | Met             | Met             | Met             | Met             | Leu        | Met             | Leu             | Met             | Leu             |                 | 1               | Met             |                 |                 |
| 13                     | GIn             | Gln             | Gln             | Gln             | 1               | Gln             | Gln             | Gln             | Gln             | Gln             | Gln        | GIN             | GIn             | GIN             |                 | Gln             | Gln             |                 | Glu             | Glu             |
| 12                     | Lys             | 1               | LVS             | Lys             | Lys        | Lys             | Lys             | Lys             | Lys             | Lys             | Lys             | Lys             | ,               | Lys             |
| -                      | Ser             |                 | Ser        | Ser             | Ser             | Ser             | Ser             | Ser             | Ser             | Ser             | Ser             | Ser             |
| 10                     | Leu             | ren             | ren             | Leu             | ne              | ren             | ren             | ren             | Ala             | ren             | ren        | ren             | ren             | Leu             | ren             | ne-             | en              | ren             | Leu             | Leu             |
| 6                      | Asp             | Asp             | Asp             | Ala             | Asp             | Asp             | Asp             | Ala             | Asp             | Asp             | Asp        | Asp             | Asp             | Asp             | Asp             | Asp             | Asp             | Asp             | Asp             | Asp             |
| 8                      | Ser             | Ser             | Ser             | Ser             | Ser             | Ser             |                 | Ser             |                 | . '             |            | Ser             | Ser             | Ser             | Ser             | Ser /           | Ser /           | Ser /           | Ser /           | Ala /           |
| _                      | Thr             | Thr        | Thr             | Thr             | Thr             | Thr             | Thr             | [hr             | Ser             | Ser             | Thr ,           |
| 9                      | Phe             |                 |            | Phe             | Phe             | Phe             | Phe .           | Nala            | Nala            | Phe             |                 | Phe             |
| 2                      | Th              |                 | Thr             |                 |                 | Th              |                 |                 | Thr             |                 |            |                 |                 | Ala             |                 | Thr             | -3              |                 |                 | Thr             |
| 4                      | Gly             | Gly             |                 | Gly             | Glý             | Gly             |                 | G)              | g<br>g          | Glý             | Gly        | <u>a</u>        | Glý             | <u>G</u>        | Gly (           | Glý             | Gly             | Gly             | Gly             | Gly             |
| က                      | Glu             | Ala             | Glu Ala         | Glu             | Olu<br>Glu      | - 1             | 1               | Olu<br>Glu      |                 | - 1             | Olu<br>Glu | Asp (           | Asp (           | Asp (           | Asp (           |                 | Asp (           | Asp (           | Asp (           | Asp (           |
| 2                      | Gly             | Gly ,           | Gly             | Gly             | Gly             | Gly             | - 1             |                 | T               |                 | ` '        | Gly ,           |                 | gly /           | Gly             | Gly /           | Gly /           | Gly             | - 1             | Gly<br>Gly      |
| +                      |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |            |                 | - 1             |                 |                 |                 |                 |                 | - 1             |                 |
| Amino Acid<br>Position | Compound 70 Ala | Compound 71 His | Compound 72 His | Compound 73 HIS | Compound 74 Ala | Compound 75 His | Compound 76 His | Compound 77 His | Compound 78 His | Compound 79 Ala |            | Compound 81 Ala | Compound 82 Ala | Compound 83 Ala | Compound 84 Ala | Compound 85 Ala | Compound 86 Ala | Compound 87 Ala | Compound 88 Ala | Compound 89 Ala |

Fig. 4E1

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|                   |                                       |                             |                                 |                             | <del></del>                           |                             |                             | .,                          |                                 | -                                       | .,                         | <del></del>                                 |                             | _                               |                             |                                 | <del>,</del>                    | 7                           | -                               |                             | <del>,</del>                |
|-------------------|---------------------------------------|-----------------------------|---------------------------------|-----------------------------|---------------------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------------------|---|----------------------------|---|-----------------------------|---------------------------------|-----------------------------|---------------------------------|---------------------------------|-----------------------------|---------------------------------|-----------------------------|-----------------------------|
|                   | •                                     |                             |                                 |                             |                                       |                             |                             |                             |                                 |   |                            |   |                             |                                 | -                           |                                 |                                 |                             |                                 |                             |                             |
|                   | တ္တ                                   |                             |                                 |                             |                                       |                             |                             |                             |                                 |   |                            |   |                             |                                 |                             |                                 |                                 | :                           |                                 |                             |                             |
|                   | 85<br>                                |                             |                                 |                             |                                       |                             |                             |                             |                                 |   |                            |   |                             |                                 |                             |                                 |                                 |                             |                                 | ;                           |                             |
|                   | 3                                     |                             | ē                               |                             |                                       |                             |                             |                             |                                 |   |                            |   |                             |                                 |                             |                                 |                                 |                             |                                 |                             |                             |
|                   | 36                                    |                             |                                 |                             |                                       |                             |                             |                             |                                 |   |                            |   |                             |                                 |                             |                                 |                                 |                             |                                 |                             |                             |
| ı,                | 35                                    |                             |                                 |                             |                                       |                             |                             |                             |                                 |   |                            |   |                             |                                 |                             |                                 | 4                               |                             |                                 |                             |                             |
| 3                 | 34                                    |                             |                                 |                             |                                       | ·<br>·                      |                             |                             |                                 |   | -                          |   |                             |                                 |                             |                                 |                                 | 1                           |                                 |                             |                             |
| 6                 | <br>                                  |                             |                                 |                             |                                       |                             |                             | ·                           |                                 |   |                            | i   |                             |                                 |                             |                                 |                                 |                             |                                 |                             |                             |
| 3                 | 32                                    |                             |                                 |                             |                                       |                             |                             | ar.                         |                                 | -                                       |                            | ,   |                             | ·                               |                             |                                 |                                 | :.                          |                                 |                             |                             |
| [ ]               | 2                                     |                             |                                 |                             |                                       | r)                          | - ) -                       |                             |                                 |   |                            | 7.  |                             |                                 |                             |                                 |                                 |                             |                                 |                             |                             |
| 6                 | ى<br>ك                                |                             |                                 |                             |                                       |                             |                             |                             |                                 | . :                                     |                            |   |                             |                                 |                             |                                 |                                 | - 0.                        |                                 |                             |                             |
| 5                 | 67                                    | NH2                         | NH2                             | 오                           | NH2                                   | NH2                         | Z<br>Z<br>N                 | SHS.                        | NHZ                             | 汨                                       | 오                          | NH2   | H2                          | NH2                             | NH2                         | NH2                             | NH2                             | NH2                         | NH2                             | H2                          | 윞                           |
| <u> </u>          | . 7                                   | Z                           | Z                               | Z                           | Z                                     | Z                           | Z                           | Z                           | Z                               | _                                       | 4                          | 2   | $\leq$                      | <u> </u>                        | 4                           | Z                               | $\mathbf{Z}$                    | Z                           | Z                               | Z                           | Z                           |
|                   | 7 97                                  | Asn                         | Asn N                           | Asn NH2                     | Asn                                   | Asn N                       |                             | Asn                         | Asn N                           | Asn NH2                                 | Asn NH2                    | Asn N                                       | Asn NH2                     | Asn                             | Asn N                       | Asn                             | Asn N                           | Aśn N                       | Asn N                           | Asn NH2                     | Asn NH2                     |
| 6                 |                                       |                             | Lys Asn                         | Lys Asn N                   |                                       | Lys Asn N                   | Lys Asn N                   | Lys Asn N                   |                                 | Lys Asn N                               | Lys Asn N                  | Lys Asn                                     | Lys Asn N                   | Lys Asn IN                      |                             | Lys Asn N                       | Lys Asn N                       | Lys Asn N                   | ı i                             | Lys                         | Lys Asn N                   |
| 02 00             | 22                                    | Asn                         | Asn                             |                             | Asn                                   | Asn                         |                             | Asn                         | Asn                             |   |                            | Asn   | Asn                         | Asn                             | Asn                         | Asn                             | Asn                             | Aśn                         | Asn                             |                             | Leu Lys Asn N               |
| 00 00             | 87 /7                                 | Lys Asn                     | Lys Asn                         | Lys                         | Lys Asn                               | Lys Asn                     | Lys Asn                     | Lys Asn                     | Leu Lys Asn                     | Leu Lys                                 | Leu Lys                    | Leu Lys Asn                                 | Leu Lys Asn                 | Leu Lys Asn                     | Leu Lys Asn                 | Leu Lys Asn                     | Lys Asn                         | Lys Asn                     | Lys Asn                         | Leu Lys                     | Lys.                        |
| 00 00 00          | 82   73   07                          | Leu Lys Asn                 | Leu Lys Asn                     | Leu Lys                     | Leu Lys Asn                           | Leu Lys Asn                 | Leu Lys Asn                 | Leu Lys Asn                 | Leu Lys Asn                     | Leu Lys                                 | Lys                        | Leu Lys Asn                                 | Trp Leu Lys Asn             | Leu Lys Asn                     | Lys Asn                     | Leu Lys Asn                     | Leu Lys Asn                     | Leu Lys Asn                 | Leu Lys Asn                     | Leu Lys                     | Leu Lys                     |
| 20 20 20          | 97 /7 07 07                           | Phe Leu Lys Asn             | Phe Leu Lys Asn                 | Phe Leu Lys                 | Phe Leu Lys Asn                       | Trp Leu Lys Asn             | Glu Trp Leu Lys Asn         | Trp Leu Lys Asn             | Trp Leu Lys Asn                 | Trp Leu Lys                             | Trp Leu Lys                | Phe Leu Lys Asn                             | Trp Leu Lys Asn             | Phe Leu Lys Asn                 | Trp Leu Lys Asn             | Phe Leu Lys Asn                 | Trp Leu Lys Asn                 | Phe Leu Lys Asn             | Trp  Leu Lys  Asn               | Phe Leu Lys                 | Trp Leu Lys                 |
| 00 00             | 97   70   77   78                     | Glu Phe Leu Lys Asn         | Glu Phe Leu。Lys Asn             | Glu Phe Leu Lys             | Glu Phe Leu Lys Asn                   | Glu Trp Leu Lys Asn         | Trp Leu Lys Asn             | Glu Trp Leu Lys Asn         | Glu Trp Leu Lys Asn             | Ile Glu Trp Leu Lys                     | Ile Glu Trp Leu Lys        | Ile Glu Phe Leu Lys Asn                     | Ile Glu Trp Leu Lys Asn     | Ile Glu Phe Leu Lys Asn         | Ile Glu Trp Leu Lys Asn     | Glu Phe Leu Lys Asn             | Glu Trp Leu Lys Asn             | Ile Glu Phe Leu Lys Asn     | Glu Trp Leu Lys Asn             | Glu Phe Leu Lys             | Glu Trp Leu Lys             |
| 00 00 00 00       | 97   70   77   79   79   79           | Phe Ile Giu Phe Leu Lys Asn | Leu Phe Ile Glu Phe Leu Lys Asn | Leu Phe Ile Glu Phe Leu Lys | Phe IIe   Glu   Phe   Leu   Lys   Asn | Phe Ile Glu Trp Leu Lys Asn | Phe Ile Giu Trp Leu Lys Asn | Phe Ile Glu Trp Leu Lys Asn | Leu Phe Ile Glu Trp Leu Lys Asn | Phe Ile Glu Trp Leu Lys                 | eu Phe Ile Giu Trp Leu Lys | Phe Ile Glu Phe Leu Lys Asn                 | Phe Ile Glu Trp Leu Lys Asn | Leu Phe Ile Glu Phe Leu Lys Asn | Phe Ile Glu Trp Leu Lys Asn | Leu Phe Ile Glu Phe Leu Lys Asn | Leu Phe Ile Giu Trp Leu Lys Asn | Phe Ile Glu Phe Leu Lys Asn | Leu Phe Ile Glu Trp Leu Lys Asn | Leu Phe Ile Glu Phe Leu Lys | Leu Phe Ile Glu Trp Leu Lys |
| 04 00 04 05 06 04 | 7   7   7   7   7   7   7   7   7   7 | Phe Ile Giu Phe Leu Lys Asn | Leu Phe Ile Glu Phe Leu Lys Asn | Leu Phe Ile Glu Phe Leu Lys | Phe IIe   Glu   Phe   Leu   Lys   Asn | Phe Ile Glu Trp Leu Lys Asn | Phe Ile Giu Trp Leu Lys Asn | Phe Ile Glu Trp Leu Lys Asn | Leu Phe Ile Glu Trp Leu Lys Asn | Phe Ile Glu Trp Leu Lys                 | eu Phe Ile Giu Trp Leu Lys | Phe Ile Glu Phe Leu Lys Asn                 | Phe Ile Glu Trp Leu Lys Asn | Leu Phe Ile Glu Phe Leu Lys Asn | Phe Ile Glu Trp Leu Lys Asn | Leu Phe Ile Glu Phe Leu Lys Asn | Leu Phe Ile Giu Trp Leu Lys Asn | Phe Ile Glu Phe Leu Lys Asn | Leu Phe Ile Glu Trp Leu Lys Asn | Leu Phe Ile Glu Phe Leu Lys | Leu Phe Ile Glu Trp Leu Lys |
| 20 20 20          | 7   7   7   7   7   7   7   7   7   7 | Ile Glu Phe Leu Lys Asn     | Phe Ile Glu Phe Leu Lys Asn     | Phe Ile Glu Phe Leu Lys     | Ile Glu Phe Leu Lys Asn               | Ile Glu Trp Leu Lys Asn     | Ile Glu Trp Leu Lys Asn     | Ile Glu Trp Leu Lys Asn     | Phe Ile Glu Trp Leu Lys Asn     | Compound 78 Leu Phe Ile Glu Trp Leu Lys | Phe Ile Glu Trp Leu Lys    | Compound 80 Leu Phe Ile Glu Phe Leu Lys Asn | Ile Glu Trp Leu Lys Asn     | Phe Ile Glu Phe Leu Lys Asn     | Ile Glu Trp Leu Lys Asn     | Phe Ile Glu Phe Leu Lys Asn     | Phe Ile Glu Trp Leu Lys Asn     | Ile Glu Phe Leu Lys Asn     | Phe Ile Glu Trp Leu Lys Asn     | Phe Ile Glu Phe Leu Lys     | Phe IIe Glu Trp Leu Lys     |

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| DRL | US  | JOS | J. | JUS |
|-----|-----|-----|----|-----|
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|            | <i>5/</i> _  |                 |                  | ·               | <del>i -</del>   |           | <del>-,</del>   |                 |                                       |                  |             |                       |                 |                 | <u>.                                    </u> |                 |                  |                 | <u>.</u>        |          |
|------------|--------------|-----------------|------------------|-----------------|------------------|-----------|-----------------|-----------------|---------------------------------------|------------------|-------------|-----------------------|-----------------|-----------------|--|-----------------|------------------|-----------------|-----------------|----------|
| AFF        | 707          | -               | Arg              | Arg             | Ard              | Ard       | Δr              | 2 4             | Y d                                   | Arg              | Ara         | 2 5                   | ₽<br>V          | Arg             | Ara  | 2 0             | Σ<br>•           | Arg             | Arg             | VAV      |
| -          | 19           | -               | \ag              | Val             | Val              | \Za       | 2 2             | 3 3             | \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ | \<br>\<br>\      | \<br>\<br>\ | 10/2                  | <u>8</u>        | Sa<br>Sa        | Va   | /2/             | , d              | ı,              | Val             | 10/      |
|            | 18           |                 | Ma               | Ala             | Ala              | Ala       | A 2             | 2 <             | 2 2                                   | Ald              | Ala         | \<br>\<br>\<br>\<br>\ | ב<br>ב<br>י     | Ala             | Ala  | ΔI2             |                  | T               |                 |          |
|            | 17           | <u>:</u>        | ם<br>פ           | <u>n</u>        | <u>g</u> n       | <u>G</u>  | 1               | - 1             | 3 2                                   | ם<br>ס           | 35          | 1 -                   | - 1             | פות             | Glu  | 1               | $\neg$           |                 | <u></u>         | =        |
|            | 16           | 5               | 5                | <u>n</u> 5      | <u>G</u> lu      | Olu       | GIU             | 1               |                                       |                  | <u>0</u>  0 | 1 '                   |                 |                 | Glu  | 311             | - 1              |                 | <u> </u>        |          |
|            | 15           | 1               | 2 0              | <u> </u>        | glu              | Glu       | Glu             |                 |                                       | - 1              | <u>n</u> .  | 1                     | - 1             |                 | <u>B</u>                                     | 3               |                  | - 1             |                 |          |
|            | 4            | ā               | - 1              | Met             | ren              | Met       | Leu             | Met             | ā                                     | - 1              | Met         | PII GIII              |                 | ME              | Leu  | Met             | 1                |                 | Mei             | <u>-</u> |
|            | 13           | ر<br>ان         | 5 6              |                 | gu<br>Bu         | GIn       | Gln             | Gln             | - L                                   | 3 6              | <u></u>     | Gli                   | 7               |                 | 5  | G               |                  |                 |                 | A        |
|            | 12           | Λο              | 2                | r/s             | LYS              | Lys       | Lys             | Lvs             |                                       | 2                | Lys         | NS.                   |                 |                 | Lys  | Ala             |                  | ļ.              | ر<br>د<br>د     | _<br>S   |
|            | =            | Spr             | 5 6              | ) C             | Ser              | Ser       | Ser             | Ser             | Ser                                   |                  | Ser         | Ser                   | Q Q             | - 1             | Ala  | Ser             |                  |                 |                 | Ze.      |
|            | 10           | ā               | - 1              |                 | lee              | ren       | Leu             | Ala             | 1                                     |                  | L'GIY       | Palv                  | ) [             | ם ב             | ren  | ren             | ā                |                 |                 | Le       |
|            | <u>ග</u>     | Asn             | 2 <              | 2 2             | Ala              | 35        | <u>G</u> lu     | Asp             | Asp                                   | - 0              | ASP         | Asp                   | Acn             |                 |  | Asp             | Asp              | Ann             |                 | HSD      |
|            | ∞            | Ala             | Sor              | 5 0             | )<br>(A          | Ser       | Ser             | Ser             |                                       | Š                | 000         | Ser                   |                 | 5 6             |  | Ser             | Ser              | Spr             | 5 6             | )<br>(C) |
| L          |              | Th              | i<br>H           |                 | =                |           | Į.              | Thr             | Thr                                   | Thr              | =           | Thr                   | Thr             | - 1             | - 1  | i<br>i          | Thr              | Thr             | ,<br>L          |          |
| L          | 9            | Phe             | Dha              | 2 0             |                  | 7 J       | Phe             | Phe             | Phe                                   | Dho              |             | Phe                   | Phe             |                 |  | Phe             | Phe              | Phe             | D P             |          |
|            | ഹ            | Th              | Thr              | ,<br>P          |                  |           | - 1             | Thr             | Ī                                     | ا<br>ا<br>ا      |             | 1                     | Thr             | ۲<br>۲          |  | ١h٢             | Thr              | Thr             |                 |          |
| _          | 4            | <u>S</u>        | E                |                 | 5 2              | 5 0       | <u>S</u>        | gl              | <u>Ş</u>                              | 2                | 5 0         |                       | 2               | 2               | - 1  | GJ              | Gly              | <u>S</u>        | 2               | 5        |
|            | က            | Asp             | Asn              |                 |                  | ASD.      | ASD             | Asp             | Asp                                   | Acn              | 2 4         | Asp Gly               | Asp             | Ven             | 2  | ASp             | Asp              | Asp             | Acn             | 200      |
| ,          | 2            | GIS             | <u>≥</u>         | 2               | 5 C              | - 1       | - 1             | <u>2</u>        | <u>ය</u>                              | 2                | 5 2         | GIY                   | <u>G</u>        | <u>.</u><br>ان  | 5 0  | 1               | <u>G</u>         | Gly             | Gly Ash Gly     | 5        |
|            | <del>-</del> | Ala             | Ala              | Ala             | 5 2              | 2 <       |                 |                 | Ala                                   | Ala              | - 1         | - 1                   |                 | 1               |  |                 |                  |                 |                 |          |
| Amino Acid | Position     | Compound 21 Ala | Compound 22 A la | Compound 23 Ala | Compaind 24 A La | מיווים בא | Compound 23 Ala | Compound 26 Ala | Compound 27 Ala                       | Compound 28 A la |             | Compound 29 AIA       | Compound 30 Ala | Compound 31 Ala |  | Compound 32 A1a | Compound 33 A la | Compound 34 Ala | Compound 35 Ala |          |
| Am         | ٩            | Com             | Som              | S               | Š                |           | 3 ,             | 5               | Sem                                   | Com              | ,           | 5                     | 12<br>12        |                 |  | 3               | Comp             | Comp            | Comp            |          |
|            |              |                 |                  |                 |                  |           |                 |                 |                                       |                  |             |                       |                 |                 |  |                 |                  |                 |                 |          |

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| Amino Acid | 0       |            | [ ]      |         |              |      |             |             |    |      |              |    |    |    |    |    |     | ٠. |   |
|------------|---------|------------|----------|---------|--------------|------|-------------|-------------|----|------|--------------|----|----|----|----|----|-----|----|---|
| 77         | ·-      | 22         | 24       | 52      | 56           | 27   | 28          | 53          | 30 | 31   | 32.          | 33 | 34 | 35 | 36 | 37 | 38  | 39 |   |
| Phe        |         | ⊟e         | 긢        | Phe     | ē            | S/   | Asn         | NHS         |    |      |              |    |    |    |    |    |     |    |   |
| Phe        |         | lle<br>Ile | Glu      |         |              | - 1  | - 1         | N C         |    | e .  |              |    |    |    | `  |    |     | a  |   |
| <u>a</u>   |         | Ile        | 1 1      |         | $T^{-}$      |      | Acn         | N S         |    |      |              |    |    |    |    | 1  | *   |    |   |
| □          | Phe     | Ile        | 1        |         |              | S S  | LVS ASh NH2 | N. S. L.    |    |      |              |    |    |    |    |    |     | ,  |   |
| ď          | Phe IIe |            | Glu      | Phe     | <del> </del> | NS N | Asn         | Į<br>Į      |    |      |              |    |    |    |    |    | -   |    |   |
| ш.         | Phe IIe |            | Gla      | le<br>E | <del></del>  | LVS  | Asn         | 子<br>子      |    |      |              |    |    |    |    |    |     |    |   |
| ш_         | Phe ]   | e          | Gla      |         | 1            | LVS  |             | N<br>F      |    |      |              |    |    |    |    |    |     |    |   |
|            | Phe I   | lle        | 35       |         | 1            | SX.  | Asn         | F S         |    |      |              | 1  |    |    |    |    | 0   |    |   |
| _          | Phe I   | lle (      | 35       | Phe     |              | S S  | Agn         | NHO         | 1  |      |              |    |    |    |    |    |     |    |   |
|            | Phe I   | elle       | JE<br>B  |         |              |      | Acn         | NHO         |    | -  - |              |    |    |    |    |    |     |    | , |
|            | Phe I   | le<br>le   | <u> </u> | 1       | G            |      | Asn         | NHO         |    |      |              |    |    |    |    |    |     | -  |   |
|            | Phe I   | lle (      | 등        |         | 1            | SA   |             | 1 SE        | -  |      |              |    |    |    |    |    | *   |    |   |
| 14.        | Phe I   | Ile        | Oll I    | 1       |              | 1    | Asn NH2     | 15          |    |      |              |    |    | •  |    |    |     |    |   |
| Ω          | Phe II  | lle        | J<br>J   |         | 1            |      | Asn         | 를<br>된<br>된 | +  |      |              |    |    |    |    |    |     |    |   |
| n          | Phe II  |            | 3        | Phe     | 1            | No.  |             | NHO         | -  |      | -            |    | 1  | +  |    |    | ı X |    |   |
| Į          |         |            |          |         | 3            |      | 2           | 7 1         |    |      | <del>.</del> |    | -  |    | •  |    | -   |    |   |

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|          | <del></del>                             |  |   |   |  |   |   |  |   |  |  |  |   |  |  |  | _   |  |  | . /  |  |  |  |
|----------|---|--|---|---|--|---|---|--|---|--|--|--|---|--|--|--|---|--|--|--|--|--|--|
| 20       | 1.                                      | Arg  | Arg   | Arg   | Arg  | Arg   | Arg   | Arg  | Ard   | Ara  | 5 4  | Arg.   | Arg   | Arg  | Ala  | Ala  | Arg   | Ara  | ה<br>ל   | Σ <  | Arg  | Arg .  | Arg  |
| 19       |   |  |   | <u>a</u>  | <u>a</u>   | \a<br>\   | Val   | Val  | Val   | \<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\  | 3 3  | ا<br>د<br>د  | Ala   | Ala  | Val:   | Val  |   |  | $\top$   |  |  | _   _  |  |
| 78       | -                                       | Ala<br>•   | Ala   | Ala   | Ala  | Ala   | - 1   |  | Ala   | Ala  | $\neg$   | $\Box$   |   |  | l  | 1  |   | Γ  |  |  |  |  |  |
| 17       |   |  |   |   |  |   |   |  |   |  |  |  |   |  |  |  |   |  | 1  |  |  |  |  |
| 16       |   |  |   |   | 1.1  |   |   |  |   |  |  | $\neg \top$  |   |  |  |  |   |  | T  | 7  |  |  |  |
| 5        |   |  |   |   |  |   |   | ٠ ا  |   | 1  | Τ.   | $\neg \neg$  |   |  |  |  |   | . –  |  | 1  |  | 5 C  | 5  |
|          |   | ם<br>C   | ם כ   |   | ) <  |   |   |  |   | ,  |  |  |   |  |  |  |   |  |  |  |  | 5 0  |  |
|          |   | C <  | <b>Z</b>  | 5 c   | 5 2  |   |   | - 1  |   |  | _  |  |   |  |  | _  |   |  |  | 1  | - 1  |  | - 1  |
|          |   | ت ر<br>د   | ت<br>ا<br>ا   |   | 1  | .   | - 1   |  |   |  |  |  | - 1   |  | $\neg$   | - 1  |   |  |  | 7  |  |  | 7  |
|          |   | ֓֞֞֞֞֜֞֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓֓   | 10 12   |   |  |   |   |  |   |  | 1  | $\neg$   |   |  |  |  |   |  |  | 1  | _  |  | -  |
| <u> </u> |   |  | 3 14 3  |   | 2 G  | 1.  | - 1   | - 1  |   |  |  |  | - 1   | - 1  | Ser  | Ser  | Sec   | Ser  | Ser  | Ser  | Ser  | Ser  |  |
| 9        | <del>a</del>                            |  | ] <u>a</u>  |   |  | <u>' -</u>  |   |  |   |  |  |  |   |  | Leu  | _4:  |   | ren  | Leu  | Leu  | لبندا  |  |  |
| တ        | Asp                                     |  | Ash   | _   |  | Asn   | V 0 0   | 200  | ASD.  | Asp  | Asp  | Asn  | V 00 V  | 700  | ASD  | ASD  | ASD   | Asp  | Asp  | Asp  | Asp  | Asp  | ł  |
| ∞        | Ser                                     | Ser  | Ser   | Ser   | Ser  | S   | S   | 5 2  | Sec   | Ser  | Ser  | Ser  | Spr   | 2 6  | O G  | Ser C  | Zer.  |  |  |  |  | er   |  |
| _        | 트                                       | Thr  | ĮĘ.   | JE I  | F  | Thr   | Ä   | - 1  | - 1   | - 1  |  | 1  | 1 -   | - 1  | 1  | Т  |   |  |  |  |  | -  |  |
| ဖ        | Phe                                     | Phe  | Phe   | Phe   |  | Phe   | _   |  |   | -  |  | 7  |   |  |  |  |   |  |  |  |  |  |  |
| ۍ        |   | ł  | 1   |   |  | 1   |   | 1.   |   |  |  |  |   |  |  | - 1  |   |  | 1  |  |  |  |  |
| 4        |   | ŀ  |   | 1   |  | 1   | 1   | 1  |   | -  |  | -  | <del>''</del>   | - -  | -   -  |  |   | -  |  | <u> </u>   |  |  |  |
| n        |   |  | ) ds  | ds  |  |   | Sp  |  |   | 3  | ၁<br>g   |  |   |  | 3 6  | אר ה<br>מי   | 2 5   | 2 1  | 2  | g<br>G   | g<br>G   | g<br>G   |  |
|          |   | 1  |   |   |  |   | 1   | \ <u>\</u> >   | < <   | ζ <<br>> :   |  |  | 1   | ]  |  | - 1  |   |  |  | - 1  | - 1  |  |  |
| -        |   |  |   |   |  |   | ı   | 1 -  | - 1   | -  | $\neg$   |  |   |  |  | 1  | 1   |  |  | . Т  |  |  |  |
| _        | 105 A I                                 | 106 A  | 107 A J   | 108 A I   | 109 A I  | 110 A I.  | 11 A  | 12 A I   | 12 🛕  | 2 7  | 4 A I  | 15 A ć   | 16 Als  | 17 A 12  | 18 A I   | 19 A 12  | 20 A 12   | \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \  | 2 3  | 2 Ala  | 3 A la   | AAla   |  |
| ositio   | punodu                                  | punodu   | punod   | punod   | punod  | punodi  | ponud   | ponud 1  | Doi 100   | יייייייייייייייייייייייייייייייייייייי   | bonnod   | pound 1  | pound 1   | 20und  | xound 1  | xound 1  | xound 1   | y pulled 1,  |  | ound 1;  | 2 pung   | ound 1;  |  |
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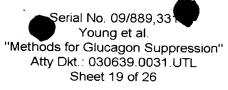
|         |                                  | 7                               | $\neg$                      | $\overline{}$               |                             | _                              | —                           | 7                           |                             | . 1                             |                                 |                             | <del>-   -</del>            |                             |                             | 7                           | · -                         | <del></del>                  |                              | <del></del>                 | <del></del>                 |
|---------|----------------------------------|---------------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------------------|---------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|------------------------------|------------------------------|-----------------------------|-----------------------------|
| DEN     | METER                            |                                 | -                           |                             |                             |                                |                             |                             | 1                           |                                 | (-                              |                             |                             |                             |                             |                             |                             |                              |                              |                             |                             |
|         | 39                               |                                 |                             |                             |                             |                                |                             |                             |                             |                                 |                                 |                             |                             |                             |                             |                             |                             |                              | 1                            |                             |                             |
|         | 38                               |                                 |                             |                             |                             |                                |                             |                             |                             |                                 |                                 |                             |                             |                             |                             |                             |                             |                              |                              |                             |                             |
|         | 37                               |                                 | *                           |                             |                             |                                |                             |                             |                             |                                 |                                 |                             | 1.                          |                             |                             | 7.                          |                             |                              | 1                            |                             |                             |
|         | 36                               |                                 |                             |                             |                             |                                |                             |                             |                             |                                 |                                 |                             |                             |                             |                             |                             |                             |                              |                              | 1                           |                             |
|         | 35                               |                                 |                             |                             |                             | : :                            |                             |                             |                             |                                 |                                 |                             |                             |                             | a .                         |                             |                             |                              |                              |                             |                             |
|         | 34                               |                                 |                             |                             |                             |                                |                             | i                           | 1."                         |                                 |                                 |                             |                             | 1                           |                             |                             |                             |                              |                              | -                           |                             |
|         | 33                               |                                 |                             |                             |                             | 1                              |                             |                             | :                           |                                 |                                 |                             |                             |                             | -                           | <b> </b>                    |                             |                              |                              |                             |                             |
|         | 32                               |                                 |                             |                             |                             |                                |                             |                             |                             | -                               |                                 |                             | -                           |                             |                             |                             |                             |                              |                              |                             |                             |
|         | 31                               |                                 |                             |                             |                             |                                |                             |                             |                             |                                 |                                 |                             |                             | -                           |                             |                             |                             |                              |                              |                             |                             |
|         | 30                               |                                 |                             |                             |                             |                                |                             |                             |                             |                                 |                                 |                             | -                           | . 181                       | -                           |                             |                             |                              |                              |                             |                             |
|         | 29                               | NF2                             | 우                           | NH2                         | 악                           | NH2                            | 2                           | 2                           | 2                           | 24                              | 24                              | 2                           | 2                           | 악                           | 2                           | 2                           | 2                           | 2                            | 2                            | 2                           | 2                           |
| - (     | CA                               | $\mathbf{z}$                    | Z                           | 之                           | 乭                           | 一                              | 巨                           | 一                           |                             | <b> </b>                        | 一                               | 步                           | 一                           | 一                           | 一                           | 三                           | 一                           | 三                            | 三                            | 三                           | 三                           |
| ,<br> - | 28                               | 1                               | Asn N                       | Asn Ni                      |                             |                                | Asn NH2                     | Asn NH2                     | Asn NH2                     | Asn NH2                         | Asn NH2                         | Asn NH2                     | Asn NH2                     | Asn NH2                     | Asn NH2                     | Asn NH2                     | Asn NH2                     | Vsn NH2                      | Vsn NH2                      | NSN NH2                     | N UN                        |
|         |                                  | Asn                             | Lys Asn NH2                 | Asn                         | Asn                         | Asn                            | Asn                         | Asn                         | Asn                         | Asn                             | Asn                             | Asn                         | Asn                         | Asn                         | Asn                         | Asn                         | Asn                         | Asn                          | Asn                          | Asn                         |                             |
|         | 27   28                          | Lys Asn                         | Lys                         | Lys Asn                     | Lys Asn                     | Lys Asn                        | Lys Asn                     | Lys Asn                     | Lys Asn                     | Lys Asn                         | Lys Asn                         | Lys Asn                     | Lys Asn                     | Lys Asn                     | Lys Asn                     | Lys Asn                     | Lys Asn                     | Lys Asn                      | Lys Asn                      | Lys Asn                     | Lys                         |
|         | 78                               | Asn                             | Leu Lys                     | Leu Lys Asn                 | Leu Lys Asn                 | Leu Lys Asn                    | Leu Lys Asn                 | Leu Lys Asn                 | Leu Lys Asn                 | Leu Lys Asn                     | Leu Lys Asn                     | Leu Lys Asn                 | Leu Lys Asn                 | Leu Lys Asn                 | Leu Lys Asn                 | Leu Lys Asn                 | Leu Lys Asn                 | Leu Lys Asn                  | Leu Lys Asn                  | Leu Lys Asn                 | Leu Lys                     |
| -       | 26   27   28                     | Trp Leu Lys Asn                 | Phe Leu Lys                 | Trp Leu Lys Asn             | Phe Leu Lys Asn             | Trp Leu Lys Asn                | Phe Leu Lys Asn             | Trp Leu Lys Asn             | Phe Leu Lys Asn             | Trp Leu Lys Asn                 | Phe Leu Lys Asn                 | Trp Leu Lys Asn             | Phe Leu Lys Asn             | Trp Leu Lys Asn             | Phe Leu Lys Asn             | Trp Leu Lys Asn             | Phe Leu Lys Asn             | Trp Leu Lys Asn              | Phe Leu Lys Asn              | Trp Leu Lys Asn             | Phe Leu Lys                 |
|         | 25 26 27 28                      | Glu Trp Leu Lys Asn             | Glu Phe Leu Lys             | Glu Trp Leu Lys Asn         | Glu Phe Leu Lys Asn         | Glu Trp Leu Lys Asn            | Glu Phe Leu Lys Asn         | Glu Trp Leu Lys Asn         | Glu Phe Leu Lys Asn         | Glu Trp Leu Lys Asn             | Glu Phe Leu Lys Asn             | Glu Trp Leu Lys Asn         | Glu Phe Leu Lys Asn         | Glu Trp Leu Lys Asn         | Glu Phe Leu Lys Asn         | Glu Trp Leu Lys Asn         | Glu Phe Leu Lys Asn         | Glu Trp Leu Lys Asn          | Glu Phe Leu Lys Asn          | Glu Trp Leu Lys Asn         | Glu Phe Leu Lys             |
|         | 24 25 26 27 28                   | Ile Glu Trp Leu Lys Asn         | Ile Glu Phe Leu Lys         | Ile Glu Trp Leu Lys Asn     | Ile Glu Phe Leu Lys Asn     | Ile Glu Trp Leu Lys Asn        | Ile Glu Phe Leu Lys Asn     | Glu Trp Leu Lys Asn         | Glu Phe Leu Lys Asn         | Ile Glu Trp Leu Lys Asn         | Ile Glu Phe Leu Lys Asn         | Ile Glu Trp Leu Lys Asn     | Ile Glu Phe Leu Lys Asn     | Ile Glu Trp Leu Lys Asn     | Ile Glu Phe Leu Lys Asn     | Ile Glu Trp Leu Lys Asn     | Ile Glu Phe Leu Lys Asn     | lle Glu Trp Leu Lys Asn      | Ile Glu Phe Leu Lys Asn      | Val Glu Trp Leu Lys Asn     | Val Glu Phe Leu Lys         |
|         | 22   23   24   25   26   27   28 | Phe Ile Glu Trp Leu Lys Asn     | Phe Ile Glu Phe Leu Lys     | Phe Ile Glu Trp Leu Lys Asn | Phe Ile Glu Phe Leu Lys Asn | Phe Ile Glu Trp Leu Lys Asn    | Phe Ile Glu Phe Leu Lys Asn | Phe Ile Glu Trp Leu Lys Asn | Phe Ile Glu Phe Leu Lys Asn | Phe lie Glu Trp Leu Lys Asn     | Phe Ile Glu Phe Leu Lys Asn     | Phe Ile Glu Trp Leu Lys Asn | Phe lie Glu Phe Leu Lys Asn | Phe Ile Glu Trp Leu Lys Asn | Phe Ile Glu Phe Leu Lys Asn | Phe Ile Glu Trp Leu Lys Asn | Phe Ile Glu Phe Leu Lys Asn | Nala Ile Glu Trp Leu Lys Asn | Nala Ile Glu Phe Leu Lys Asn | Phe Val Glu Trp Leu Lys Asn | Phe Val Glu Phe Leu Lys     |
|         | 21 22 23 24 25 26 27 28          | Leu Phe Ile Glu Trp Leu Lys Asn | Leu Phe Ile Glu Phe Leu Lys | Phe Ile Glu Trp Leu Lys Asn | Phe Ile Glu Phe Leu Lys Asn | eu Phe Ile Glu Trp Leu Lys Asn | Phe Ile Glu Phe Leu Lys Asn | Phe Ile Glu Trp Leu Lys Asn | Phe Ile Glu Phe Leu Lys Asn | Leu Phe Ile Glu Trp Leu Lys Asn | Leu Phe Ile Glu Phe Leu Lys Asn | Phe Ile Glu Trp Leu Lys Asn | Phe lie Glu Phe Leu Lys Asn | Phe Ile Glu Trp Leu Lys Asn | Phe Ile Glu Phe Leu Lys Asn | Phe Ile Glu Trp Leu Lys Asn | Phe Ile Glu Phe Leu Lys Asn | Nala Ile Glu Trp Leu Lys Asn | Nala Ile Glu Phe Leu Lys Asn | Phe Val Glu Trp Leu Lys Asn | Leu Phe Val Glu Phe Leu Lys |
|         | 21 22 23 24 25 26 27 28          | Phe Ile Glu Trp Leu Lys Asn     | Leu Phe Ile Glu Phe Leu Lys | Phe Ile Glu Trp Leu Lys Asn | Ile Glu Phe Leu Lys Asn     | Phe Ile Glu Trp Leu Lys Asn    | Ile Glu Phe Leu Lys Asn     | Glu Trp Leu Lys Asn         | Glu Phe Leu Lys Asn         | Phe lie Glu Trp Leu Lys Asn     | Phe Ile Glu Phe Leu Lys Asn     | Ile Glu Trp Leu Lys Asn     | Phe lie Glu Phe Leu Lys Asn | Ile Glu Trp Leu Lys Asn     | Phe Ile Glu Phe Leu Lys Asn | Phe Ile Glu Trp Leu Lys Asn | Phe Ile Glu Phe Leu Lys Asn | Nala Ile Glu Trp Leu Lys Asn | Ile Glu Phe Leu Lys Asn      | Val Glu Trp Leu Lys Asn     | Phe Val Glu Phe Leu Lys     |



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|                        |                                       | <b></b>          |                  |                  |                  |                  |                  |                  |                  |            |                  | <del></del>      |                  |                  |                  |       |                  |                              |
|------------------------|---------------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------|------------------|------------------|------------------|------------------|------------------|-------|------------------|------------------------------|
| 20                     | \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ | Σ <              | 2 <              | 2 5              | 2 6              | 2 2              | ל ל              | δ <b>γ</b>       | Arg              | Ard        | Δro              | 2 0              | ָר ל<br>ט        | ٦<br>۲           | Arg              | Ara   | Ara              | , <                          |
| 9                      | 5                                     | א א<br>א         | 2 2              | 2 2              | 2 2              | <u>a</u> 2       | 2 2              | g   3            | ਰ<br>^           | Val        | /2               | 2   10           | 3 5              | ے<br>ا           | \a<br>\a         | Val   | le/              | T                            |
| 48                     | 0 0                                   | 2 0              | ν   Δ            | Z Z              | Δ <u>Δ</u>       | N C              | A lo             | 2 2              | Ald              | Ala        | Ala              | A   A            | 7 0              |                  | Ala              | Ala   | Ţ                | 1                            |
| 17                     | GIA LIE                               | ב<br>ט           |                  | j                |                  | i                |                  |                  | 2 5              | Glu        | GIII             | 1                | - 1              | i                | T                | 200   | Glu              | 1 - 6                        |
| 16                     | =                                     | 1.               |                  |                  |                  | - 1              |                  | 1                | $\neg \tau$      | 35         | Glu              |                  |                  | 7                |                  |       | Ole<br>Ole       | - L                          |
| 15                     | 3.1                                   |                  | 7                | ,                |                  | - 1              |                  | - 1              | i                | Glu        | Glu              | 1                |                  | -                | - 1              | 200   | Glu              | 11.5                         |
| 14                     | Met                                   | 1                | - 1              |                  |                  | _                |                  | ā                | 3                | Met        | Leu              | Met              |                  |                  |                  | ren   | Met              | Mot                          |
| 13                     | G                                     | GIN              | GIn              | GIN              | 1                | 1                | 1 -              | - 1 -            | 5 6              | Gl         | GIN              | GIn              |                  |                  |                  | GIN   | GIn              | Gln                          |
| 12                     | LVS                                   | LVS              | LVS              | L/S              | Lvs              | Lys              | 1 -              | 1                | - 1              | Lys        | Lys              | LVS              |                  |                  | 1                | Lys   | Lys              | SA                           |
| =                      | Ser                                   | Ser              | Ser              | Ser              | Ser              | Ser              | Ser              | Spr              | 5                | Ser        | -en Ser          | Ser              | Ser              |                  | _                | Ser   | Ser              | Ser                          |
| 2                      | Leu                                   | Leu              | Leu              | Leu              | Leu              | Leu              | Leu              |                  |                  | Leu        | ren.             | Leu              | Leu              |                  |                  | Teg   | Leu              | Leu                          |
| 6                      | Asp                                   | Asp              | Asp              | Asp              | Asp              | Asp              | Asp              | Asp              |                  | ASp        | Asp              | Asp              | Asp              | Asn              | 2 1              | ASD   | Asp              | Ala                          |
| 80                     | Ser                                   | Ser              | Ser              | Ser              | Ser              | Ser              | Ser              | Ser              | - 1              |            | Ser              | Ser              | Ser              |                  |                  | - 1   |                  | Ser                          |
| 7                      | Į.                                    | Thr              | Thr              | THE              | Thr              | Thr              | Thr              | Thr              | 1                | - 1        |                  | Thr              | Thr              | Thr              |                  |       |                  | 그                            |
| 9                      | Phe                                   | Phe              | Phe              | Phe              | Phe              | Phe              | Phe              | Phe              | Dho              | alle<br>L  | Phe              | Phe              | Phe              | Phe              |                  |       | Phe              | Phe                          |
| 5                      | 重                                     | Thr              | İ                |            |                  | Thr              | Thr              | Thr              | 1                | - 1   | - 1              | Ë                            |
| 4                      | <u>S</u>                              | Gly              | Gly              | Gly              | Gly              | Gly              | Gly              | G<br>S           | ) [              |            |                  |                  |                  |                  | Т                | 7     |                  |                              |
| က                      | Asp (                                 | Asp              | Asp              | Asp              | Asp              | Asp              | Asp (            | Asp Gly          | Aca Cla          | ر<br>ارولا | Asp Gly          | Asp Gly          | Asp              | Glu Gly          | A12 C1V          | מול ל | GIU Ala          | Glu                          |
| 2                      | GlŚ                                   | Gly              | <u>:</u>         |            | GIŞ              | Gly              | Gly Asp Gly      | Gly              | <u>-</u>         |       | 25               | Compound 140 HIS GIY GIU GIY |
| <del></del>            | Compound 125 Ala                      | Ala              | Ala              |                  |                  |                  | ]                |                  |                  |            | ,                |                  |                  | !                | 1                |       | S                | HIS                          |
| Amino Acid<br>Position | und 125                               | Compound 126 Ala | Compound 127 Ala | Compound 128 Ala | Compound 129 Ala | Compound 130 Ala | Compound 131 Ala | Compound 132 Ala | Commund 133 A La | 3          | Compound 134 Ala | Compound 135 Ala | Compound 136 Ala | Compound 137 Ala | Compound 138 His | 3     | Compound 139 HIS | 140<br>140                   |
| Amin<br>Pos            | Сотро                                 | Сощро            | Compo            | Сошрог           | Compor           | Compor           | Сотрог           | Сощрог           | Compo            | 3 6        | Compo            | Compor           | Сотро            | Compou           | Сошво            |       |                  | Compou                       |

Fig. 4F3



| HOV I TO | Atty Dkt.: 030639.0031.UTL<br>Sheet 19 of 26 |              |                  |              |              |                  |              |              |              |                  |              |                  |                  |              |              |                  |                  |
|----------|--|--------------|------------------|--------------|--------------|------------------|--------------|--------------|--------------|------------------|--------------|------------------|------------------|--------------|--------------|------------------|------------------|
| TRADE    |  |              |                  |              |              | 1                |              | •            | 1            | ,                | T            | T                | Ť                | - 2          | T            |                  | 1                |
|          | 39   |              |                  |              |              |                  |              |              |              |                  |              |                  |                  | NHO          | NHO          | 7                |                  |
|          | 38   |              |                  |              |              |                  |              |              |              |                  |              |                  |                  | Pro          |              | _                | !                |
|          | 37   |              |                  |              |              | 1                | ,,           |              |              |                  |              |                  | ī                | Pro          |              | $\neg$           | +                |
|          | 36   |              |                  |              |              |                  |              |              |              |                  |              |                  |                  | Pro          |              |                  |                  |
|          | 35   |              |                  | -            | ).<br>       |                  |              |              |              |                  |              |                  |                  | Ala          |              |                  |                  |
|          | 34   |              |                  |              |              |                  |              |              |              |                  |              |                  |                  | SIV<br>GIV   | 1.           |                  | <u>Ş</u>         |
|          | 33   | <u> </u>     |                  |              |              |                  |              | -            |              |                  |              |                  |                  | Ser          | 1            |                  | Ser              |
| A        | 32   |              |                  |              |              |                  |              |              |              |                  |              |                  |                  | Ser          |              |                  | Ser              |
|          | 31   |              |                  |              |              |                  |              |              |              |                  | ,            |                  | 1)               | Pro          | Pro          | Po               | Pro              |
|          | 30   |              | i                |              |              |                  | 10           |              |              |                  |              |                  | 2                | GIV          | GÍ           | ट्टे             | Gly              |
|          | 29   | N<br>F<br>S  | NHZ              | NF2          | NFS          | NHZ              | NH2          | NHZ          | NHZ          | NF2              | NH2          | NH2              | NH2              | Gly          | Gly          | g                | Gly              |
|          | 28   | Asn          | Asn              | Asn          | Asn          | Asn              | Asn          | Asn          | Asn          | Asn              | Asn          | Ala              | Ala              | Asn          | Asn          | Asn              | Asn              |
| ***      | 27   | Lys          | Lys              | Lys          | Lys          | Lys              | Lys          | Lys          | Lys          | Ala              | Ala          | Lys              | Lys              | Lys          | Lys          | Lys              | Lys              |
|          | 26   | Fe           | Leu              | Fen          | Leu          | Fe<br>Fe         | Leu          | Ala          | Ala          | <u>B</u>         | Leu          | Leu              | Fe               | Leu          | ren          | nəŋ              | Leu              |
|          | 25   | Ē            | Phe              | Trp          | Phe          | Ala              | Ala          | Trp          | Phe          | E                | Phe          | g.               | Phe              | Trp          | Phe          | Tro              | E                |
|          | 24   | 흥            | Glu              | Asp Trp      | Asp          | Glu              | Glū          | Glū          | <u> </u>     | <u>명</u>         | Glu          | Glu              | Oll<br>Oll       | Glu          | O<br>O       | 믕                | 믕                |
|          | 23   | \$           | Phe tGly Glu     | Ile          | Ile          | Ile              | Ele<br>Ele   | Ile          | Ile          | Ile              | Ile          | Ile              | Ile              | Ile          | ][e          | Ile              | Ile              |
|          | 22   | Phe          | Phe              | Phe          | Phe          | Phe              | Phe          | Phe          | Phe          | Phe              | Phe IIe      | Phe              | Phe              | Phe          | Phe          | Phe              | Phe              |
|          | 21   | Leu          | Leu              | Leu          | Leu          | Leu              | Fe           | ren          | ren          | ne-]             | ren          | Leu              | ren              | Leu          | Ten Len      |                  |                  |
| *        | Amino Acid<br>Position                       | Compound 125 | Compound 126 Leu | Compound 127 | Compound 128 | Compound 129 Leu | Compound 130 | Compound 131 | Compound 132 | Compound 133 Leu | Compound 134 | Compound 135 LeU | Compound 136 Leu | Compound 137 | Compound 138 | Compound 139 Leu | Compound 140 Leu |

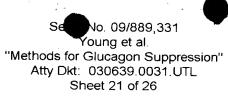
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### Serial No. 09/889 Young et al. nethods for Glucagon Suppression" Atty Dkt.: 030639.0031.UTL

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|-----|-------|-------|-----|
| She | et 20 | of 26 |     |

| Amino Acid 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 Compound 141 Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 142 Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 143 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 143 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 143 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 143 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 143 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 143 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 143 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 143 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 143 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 154 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 154 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 155 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 155 His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 155 His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Compound 155 His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Ala Val Arg Compound 155 Ala Gly Glu Gly Ala Wal Arg Compound 155 Ala Gly Glu Gly Ala Wal Arg Compound 155 Ala Gly Glu Gly Ala Wal Arg Compound 155 Ala Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Gly Ala Val Arg Compound 155 Ala Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Gly Ala Val Arg Compound 155 Ala Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Gly Ala Wal Arg Compound 155  | ,<br>      |              | ·<br>        |              |              |              |              |              | <del></del>  |              | -,           |              |              | <del></del>  |              |              | _,           |               |                | ノ   |
|--|------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|---------------|----------------|---|
| Gly Glu         Gly Thr         Phe Thr         Ser         4 Ser         10         11         12         13         14         15         16         17         18           Gly Glu         Gly Thr         Phe Thr         Ser         Asp         Leu         Ser         Lys         Gln         Leu         Glu         Glu         Glu         Ala         Ne         Glu         Ala         Ne         Glu         Glu         Glu         Glu         Glu         Glu         Ala         Ne         Glu         Glu         Glu         Glu         Ala         Ne         Ala         Ne         Glu         Glu         Glu         Ala         Ne         Glu         Glu         Glu         Ala         Ne         Ne         Ne         Ala         Ne   |            | 50           | Ara          | A            | Aro          | Aro          | A C          | Arg          | Arg          | Aro          | Ara          | Aro          | A S          | Aro          | Ara          | A S          | ν Δ<br>Σ     | A 5           | Aro            | Ard   |
| Gly Glu Gly Thr         Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Glu Ala           Gly Glu Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Glu Ala           Gly Ala Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Glu Glu Ala           Gly Ala Gly Thr         Phe Thr Ser Asp Leu Ser Lys Gl   |            | - 6          | Za<br>Za     | 29           | 200          | 5   E        | 25           | Za/          | \S           | Val          | Sa S         | le/          | S S          | \Z           | R            | 22           | 2 2          | E             | \<br> S        | \<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\<br>\ |
| 2         3         4         5         6         7         8         9         10         11         12         13         14         15         16         17         61  |            | . 8          | Ala          | 1.           | - 1          |               | Ala            | 1 1   |
| 2         3         4         5         6         7         8         9         10         11         12         13         14         15         16           Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser         Lys         Gln         Met         Glu   |            | 17           | 199          | Glu          | nl9          | 100          | Glu          | OEI<br>Cell  | Glu          | Glu          | Glu          |              |              | 7            |              |              | $\neg$       |               |                |   |
| 2         3         4         5         6         7         8         9         10         11         12         13         14         15           Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser         Lys         Gln         Leu         Glu           Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser         Lys         Gln         Leu         Glu           Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser         Lys         Gln         Leu         Glu           Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser         Lys         Gln         Glu           Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu         Ser         Lys         Gln         Met         Glu           Gly         Glu         Gly         Thr         Phe         Thr         Ser         Asp         Leu <td< td=""><td></td><td>16</td><td>ng<br/>B</td><td>Glu</td><td>Glu</td><td>35</td><td>Glu</td><td>1</td><td></td><td>1</td><td>1</td><td></td><td>Τ.</td><td>1</td><td>1</td><td></td><td></td><td></td><td>7</td><td>1</td></td<>  |            | 16           | ng<br>B      | Glu          | Glu          | 35           | Glu          | 1            |              | 1            | 1            |              | Τ.           | 1            | 1            |              |              |               | 7              | 1   |
| Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Gly Ala Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Glu Met Ala Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Asp Glu Gly Thr Ph |            | 15           |              | ]            | T            | 1.           | 1            | 1            |              | 1            |              | 1            |              | 1            |              | 1            |              |               | 1              | 1   |
| Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Gly Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Gly Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Gly Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Gly Gly Glu Gly  |            | 4            | 7            | 1            | T            | 1            |              | 1            | 1            |              | 1            |              |              |              | 1            |              |              |               |                |   |
| 2         3         4         5         6         7         8         9         10         11         12           Gly Glu Gly Thr Phe Thr Ser Asp Glu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Asp Ala Thr Phe Thr Ser Asp Leu Ser Lys Gly Asp Ala Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Cly Chy Chy Chy Chy Chy Chy Chy Chy Chy Ch  |            | <u>က</u>     |              | 1            | GIN          | 1            |              | 1            | 1            |              | 1            | 1            | 1            | 1            | 1            |              | Т            | .1            | 1              |   |
| Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Asp Ala Thr Phe Thr Ser Asp Leu Ser Gly Asp Ala Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Asp Ala Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser  |            | 12           |              | T            | 1            |              | I            | 1            |              |              |              | T            | 1            | T            | 1            | 1            | 1            | 1             |                |   |
| Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Glu Gly Thr Phe Thr Ser Asp Leu Gly Ala Gly Thr Phe Thr Ser Asp Leu Gly Ala Gly Thr Phe Thr Ser Asp Leu Gly Ala Gly Thr Phe Thr Ser Asp Leu Gly Ala Gly Thr Phe Thr Ser Asp Leu Gly Ala Gly Thr Phe Thr Ser Asp Leu  |            | <del>-</del> | 1            |              | 1            | 1            | 1            |              |              |              | ,            | 1            |              | y .          | 1            |              | 1            |               |                | į   |
| Gly Glu Gly Thr Phe Thr Ser Asp Gly Asp Ala Thr Phe Thr Ser Asp Gly Glu Gly Thr Phe Thr Ser Asp Gly Gly Ala Gly Thr Phe Thr Ser Asp Gly Gly Ala Gly Thr Phe Thr Ser Asp Gly Glu Gly Thr Phe Thr Ser Asp Gly Gly Ala Gly Thr Phe Thr Ser Asp Gly Gly Ala Gly Thr Phe Thr Ser Asp Gly Gly Ala Gly Thr Phe Thr Ser Asp Gly Gly Ala Gly Thr Phe Thr Ser Asp Gly Gly Ala Gly Thr Phe Thr Ser Asp Gly Gly Ala Gly Thr Phe Thr Ser Asp Gly Ala Gly Ala Gly Thr Phe Thr Ser Asp Gly Ala Gly Ala Gly Thr Phe Thr Ser Asp Gly Ala Gly Ala Gly Thr Phe Thr Ser Asp Gly Ala Gly Ala Gly Thr Phe Thr Ser Asp Gly Ala Gly Ala Gly Thr Phe Thr Ser Asp Gly Ala Gly Ala Gly Thr Phe Thr Ser Asp Gly Ala Gly Ala Gly Thr Phe Thr Ser Asp Gly Ala Gly Ala Gly Thr Phe Thr Ser Asp Gly Ala Gly Ala Gly Thr Phe Thr Ser Asp Gly Ala Gly Ala Gly Thr Phe Thr Ser Asp Gly Th |            |              | 1            | 1            |              | Leu          |              |              | 1            |              |              | 1            | i            | 1            | 1            |              | 1            |               |                |   |
| Gly Glu Gly Thr Phe Thr Ser  |            | တ            |              | Asp          | Asp          | Asp          | Ala          |              | Asp          | Asp          | Ala          | Asp          | Asp          | Asp          |              | Asp          | Asp          | Asp           | Asp            |   |
| Gly Glu Gly Thr Phe Thr Gly Ala Gly Thr Phe Thr  |            | œ            | Ser          | Ser          | Ser          |              |              | 1            |              |              | 1            |              | T            |              |              | •            | Ser          | 1             |                | į   |
| Gly Glu Gly Thr Phe  |            |              |              | i            |              |              |              |              |              |              |              |              | · ·          | 1            |              |              |              |               |                |   |
| Gly Glu Gly Thr Gly Ala Gly Thr Gly Ala Gly Thr Gly Ala Gly Thr  |            | ထ            | Phe          | Phe          | _            |              |              |              | -            |              |              |              |              |              |              |              |              |               | _              |   |
| Gly Glu Gly  |            | ഹ            | Thr          |              |              |              |              |              |              |              |              | ٦H           | Ę            | <b>l</b> .i  |              |              |              |               |                |   |
| 2 3 Gly Glu Gly Ala Gly Glu Gly Ala Gly Ala Gly Ala Gly Ala  |            | 4            | Gly          |              | Gly          | Ala          | Gly          | Gly          | Gly          | Ala          | Gly          |              |              | Ala          | Gly          | Gly          | Gly          | Ala           | <u>S</u>       | Gly   |
|  |            |              |              |              | - 1          |              | - 1          |              | Ala          |              | l 1          | Glu          | ŀ            | Glu .        |              |              |              | Asp           | nle<br>Oli     |   |
|  |            | 2            |              |              |              | - 1          |              | - 1          |              |              |              |              |              |              | - i          | G<br>S       | - 1          | . 1           | - 1            | Gly .   |
| Amino Acid Position Compound 141 Compound 142 Compound 145 Compound 146 Compound 146 Compound 146 Compound 146 Compound 147 Compound 150 Compound 153 Compound 153 Compound 153 Compound 153 Compound 153 Compound 154 Compound 156 Compound 15 |            | _            |              | - 1          | 1            | - 1          | - 1          | 1            | - 1          | i            | - 1          |              | His.         |              | - 1          | - 1          | - 1          | }             |                | - 1   |
|  | Amino Acid | Position     | Compound 141 | Compound 142 | Compound 143 | Compound 144 | Compound 145 | Compound 146 | Sompound 147 | Compound 148 | Compound 149 | Compound 150 | Compound 151 | Compound 152 | Compound 153 | Compound 154 | Compound 155 | conjoound 156 | Compound 157 / | ompound 158   |

Fig. 4G1



| 2          |          | · · ·        | ٠.,            |                    |                    |        |                  |                  |              |              |     |                |                  |                  |           |                |              |              |              |               |                  | <i>)</i> .       |              |          |
|------------|----------|--------------|----------------|--------------------|--------------------|--------|------------------|------------------|--------------|--------------|-----|----------------|------------------|------------------|-----------|----------------|--------------|--------------|--------------|---------------|------------------|------------------|--------------|----------|
| . :<br>. : |          |              |                |                    | 7                  |        |                  |                  |              |              |     |                |                  |                  |           |                |              |              |              |               |                  | 2                | Ž            | S I      |
|            | 39       |              |                |                    |                    | -      |                  |                  | ŀ            |              |     |                |                  |                  | 옷         | NHS            | 7 12         |              |              |               |                  | 2                | _            | Cor      |
|            | 38       |              |                |                    | :<br>:             |        | :                | -                |              |              | ba. |                |                  |                  | tPro      |                |              | ZUN          | . •          |               |                  | 0                |              | D<br>C   |
|            | 37       | 110          | ZUNI           |                    |                    |        |                  |                  |              |              | ٠.  |                |                  | •                | t<br>S    | Pro            | 2 2          |              | NHZ          |               |                  | 2                | 2            | 20       |
|            | 36       | 0            | 2              | 25                 | 꽃                  |        | 1 5              |                  |              |              |     |                |                  |                  | tPro tPro | tPro tPro tPro | 2 6          | ם ואום       | DF10 NH2     | NH2           |                  | D<br>C           |              |          |
|            | 35       | 2            | Z -            | Ala                | Ala                | NH2    |                  |                  |              |              | ٠.  |                |                  |                  | Ala       | Ala            |              |              | Ala          | Ala           |                  | Δla              | 2            | Ala Pro  |
|            | 34       | 2            | 5 0            | - 1                | GIV                | GIV    | NF.              | !                |              |              |     |                |                  | ٠.               | <u>S</u>  | G<br>G         | T            | Г            | <u>^</u>     | <u> </u>      |                  |                  | - 1          |          |
|            | 33       | Spr          | 5 6            | - T                | Ser                | Ser    | Ser              | SHS              | NF.          | 7            |     |                |                  |                  | Ser       | Ser            | ·            | 7            |              | Ser           |                  | Spr              | - 1          | Ser      |
|            | 32       | S.           | - 1            |                    | - 1                | Ser    | Ser              | 1                |              |              | 7 1 |                |                  | - [              | Ser       | Ser            |              | $\neg$       | ב<br>ב       | Ser .         |                  | Ser              |              | yer      |
|            | 31       | Pro          | - 1            |                    | - [                | ٦<br>0 | Pro              | Pro              |              | i            |     | N<br>F<br>S    |                  | į,               | 5         | Pro            | 1            | PDro Cor     | <u> </u>     | Pro Ser       | ZF.              | Pro              |              | 2        |
|            | 30       | )<br>O       | <u>ر</u><br>اي |                    |                    | Gly.   | GlV              | <u>Ş</u>         |              | 1 .          | - 1 | <u>ල</u>       | NH2              |                  |           | GIV            | 1            | 1            | - [          | Gly           | S<br>S           | ) Sign           |              | <u></u>  |
|            | 53       | Glv          | <u>ج</u><br>ان | -1                 |                    | gy     | Gly              | <u>Ş</u>         | è            | 1.           |     |                | 8                | Ţ-               | g<br>S    | Gly            | 3            |              |              | G<br>S        | <u>G</u>         | O<br>OS          | 1            | <u>-</u> |
|            | 28       | Asn          | Acn            |                    |                    | Asn    | Asn              | Asn              |              | Asn          |     |                | Asn (            |                  |           | Asn (          | Asn (        | Asn          |              | ı             | Asn (            |                  |              |          |
|            | 27       | Lvs          | , <u>v</u>     |                    | - 1                | Lys    | Lys              | Lys              | [\x          |              |     | Lys Asn        | Lys              | 1                | ر<br>درا  | Lys /          | Lys          | , SA         | 2            | Lys Asn       | Lys //           | Lys /            |              |          |
|            | 26       | Leu          | ā              |                    |                    | Fe     | <br>Fen          | ren              | Leu          | len          |     | =<br>공         | -<br>-<br>-<br>- | ā                | _         | ne T           | leu l        | ā            | 7            | 1<br>16<br>16 | <u> </u>         | - F              | 07           | ם<br>ר   |
|            | 25       | Phe          | ٦              | _                  |                    | 2      | E<br>E           | Trp              | Phe          | 2            |     | Pne<br>        |                  | ٤                | 7         | <u>n</u>       | <u>.e</u>    | .0           | 1            | =             | 은                | D<br>D           | Dho          |          |
|            | 24       | Glu          | GII.           | 1 2                |                    | 3      | 믮                | US               | Glu          | <u></u>      | Т   | חום            | 믕                | <u>-</u>         |           | <u>=</u>       | <u></u>      | Glu          | 5            |               |                  | Glu              | 1115         | - 1      |
|            | 23       | Ile          | <u>e</u>       | T                  | T                  | $\top$ | )<br>He          | )<br>ell         | ) ell        | lle          | Γ   | e le           |                  | )<br>i           |           | )<br>ell       | e<br>e       |              | 2            |               | Ile              | Ile (G           | Ile (C       |          |
|            | 22       | Phe          | Phe            | -                  | _                  |        | Phe              | Phe              | Phe          | Phe I        | 1   | _              | Phe I            | Phe I            | 2         | rne<br>I       | Phe I        | Phe II       | Dho 1        |               |                  | Phe              | Phe II       | <u> </u> |
|            | 21       | Leu I        | - F            |                    | 3 8                | 3      | - i              | i                | Leu          | Leu          | 100 | 3              |                  |                  | 1         | E E            | Leu<br>F     | Leu F        | ā            |               |                  | - 1              | Leu P        |          |
| _          |          |              |                | rd 143             | 4 1 1 1            | #   -  | d 145            | d 146            | ld 147       | d 148        | 000 | 2              | d 150            | d 151            | -         | 7 257          | d 153        | d 154        | 1.55         | <u> </u>      | 138<br>1         | 1157 L           | 158          | 1        |
| Amino Acid | Position | Compound 141 | Compound 142   | Compound 143   P.1 | Communication 1441 |        | Compound 145 Leu | Compound 146 Leu | Compound 147 | Compound 148 |     | Culibouila 148 | Compound 150 Leu | Compound 151 Leu | -         | Compound 1521  | Compound 153 | Compound 154 | Compound 155 |               | Compound 156 Leu | Compound 157 Leu | Compound 158 |          |

Fig. 4G2

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Compound

- 4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys-NH<sup>E</sup>octanoyl Asn-NH<sub>2</sub>
- 4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys-NH<sup>E</sup>octanoyl Asn-NH<sub>2</sub> 8
- 4-ImidazolyIpropionyi-Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys-NH $^{
  m E}$ octanoyl Asn Gly Gly-NH $_2$ 22/26
- 4-ImidazolyIpropionyI-Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys-NH<sup>E</sup>octanoyl Asn Gly Gly-NH<sub>2</sub> 162
- 4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Asn Lys-NH<sup>E</sup>octanoyl-NH<sub>2</sub> 163
- 4-ImidazolyIpropionyl-Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Asn Lys-NH<sup>E</sup>octanoyl-NH<sub>2</sub>

# Fig. 4H



Compound

4-Imidazolylpropionyl-Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Asn Lys-NH<sup>E</sup>octanoyl Gly Gly-NH<sub>2</sub>

4-ImidazolyIpropionyl-Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Asn Lys-NH<sup>E</sup>octanoyi Gly Gly-NH<sub>2</sub> 166

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp -eu Lys-NH<sup>E</sup>octanoyl Asn -NH<sub>2</sub>

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Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys-NH<sup>E</sup>octanoyl Asn -NH<sub>2</sub>

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys-NH<sup>E</sup>octanoyl Asn Gly Gly-NH<sub>2</sub> Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys-NH Eoctanoyl Asn Gly Gly-NH2

## Fig. 41

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp 171

Leu AsnLys-NH<sup>E</sup>octanoyl-NH<sub>2</sub>

Compound No.

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe

Leu Asn Lys-NH Eoctanoyl-NH2

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp

Leu Asn Lys-NH<sup>E</sup>octanoyl Gly Gly-NH<sub>2</sub>

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe

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Leu Asn Lys-NH<sup>E</sup>octanoyl Gly Gly-NH<sub>2</sub>

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### Effect of functional nephrectomy on Exendin-4 clearance

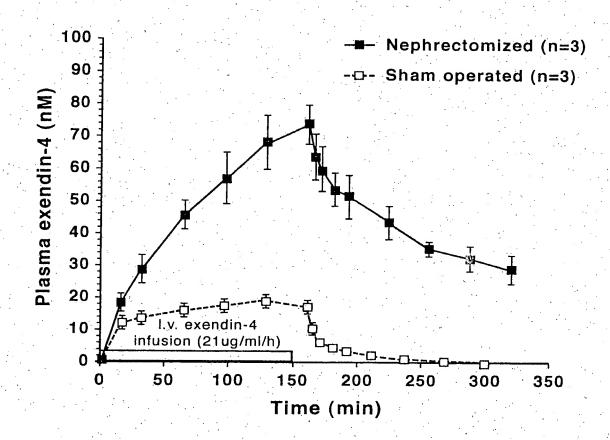


Fig. 5



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#### Terminal decay

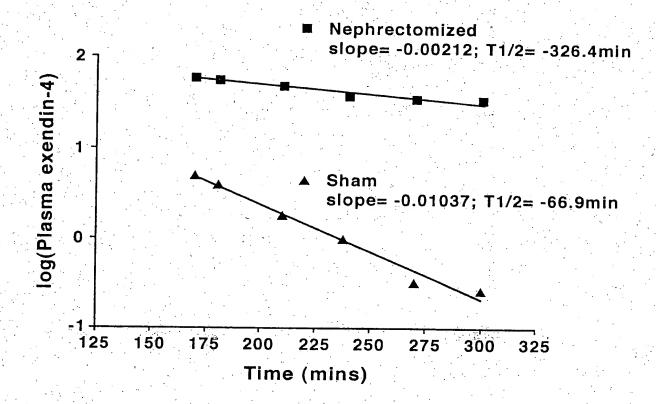


Fig. 6